PALM INTRANET

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FILE 'BIOSIS, MEDLINE, CAPLUS, EMBASE' ENTERED AT 15:28:21 ON 19 DEC 2002

L1	426	THROMBOSPONDIN 2
L2	7436	OSTEOPONTIN
L3	250	TSP2
L4	2239	OPN
L5	1046933	ANTAGONIS?
L6	77890	ANTISENS?
L7	15362	RIBOZYM?
L8	695	BLOCKING PEPTIDE
L9	15	L1 AND L5
L10	10	DUP REM L9 (5 DUPLICATES REMOVED)
L11	12	L1 AND L6
L12	6	DUP REM L11 (6 DUPLICATES REMOVED)
L13	1	L1 AND L7
L14	0	L1 AND L8
L15	10	L3 AND L5
L16	4	DUP REM L15 (6 DUPLICATES REMOVED)
L17	12	L3 AND L6
L18	4	DUP REM L17 (8 DUPLICATES REMOVED)
L19	1	L3 AND L7
L20	0	L3 AND L8
L21	276	L2 AND L5
L22	160	DUP REM L21 (116 DUPLICATES REMOVED)
L23	178	L2 AND L6
L24	73	DUP REM L23 (105 DUPLICATES REMOVED)
L25	13	L2 AND L7
L26	7	DUP REM L25 (6 DUPLICATES REMOVED)
L27	2	L2 AND L8
L28	67	L4 AND L6
L29	23	DUP REM L28 (44 DUPLICATES REMOVED)
L30	8	L4 AND L7
L31	2	DUP REM L30 (6 DUPLICATES REMOVED)
L32	0	L4 AND L8
L33	866	WOUND RESPONSE
L34	0	L33 AND L29
L35	1	L33 AND L12
L36	1	L33 AND L23
L37	0	L33 AND L28

L10 ANSWER 1 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1

ACCESSION NUMBER: 2002:363702 BIOSIS
DOCUMENT NUMBER: PREV200200363702
TITLE: Interactions of thrombospondins with alpha4beta1 integrin and CD47 differentially modulate T cell behavior.
AUTHOR(S): Li, Zhuqing; Calzada, Maria J.; Sipes, John M.; Cashel, Jo Anne; Krutzsch, Henry C.; Annis, Douglas S.; Mosher, Deane F.; Roberts, David D. (1)
CORPORATE SOURCE: (1) National Institutes of Health, 10 Center Dr., Building 10, Room 2A33, MSC 1500, Bethesda, MD, 20892-1500: droberts@helix.nih.gov USA
SOURCE: Journal of Cell Biology, (April 29, 2002) Vol. 157, No. 3, pp. 509-519. http://www.jcb.org/. print.
ISSN: 0021-9525.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Thrombospondin (TSP)-1 has been reported to modulate T cell behavior both positively and negatively. We found that these opposing responses arise from interactions of TSP1 with two different T cell receptors. The integrin alpha4beta1 recognizes an LDVP sequence in the NH2-terminal domain of TSP1 and was required for stimulation of T cell adhesion, chemotaxis, and matrix metalloproteinase gene expression by TSP1. Recognition of TSP1 by T cells depended on the activation state of alpha4beta1 integrin, and TSP1 inhibited interaction of activated alpha4beta1 integrin on T cells with its counter receptor vascular cell adhesion molecule-1. The alpha4beta1 integrin recognition site is conserved in TSP2. A recombinant piece of TSP2 containing this sequence replicated the alpha4beta1 integrin-dependent activities of TSP1. The beta1 integrin recognition sites in TSP1, however, were neither necessary nor sufficient for inhibition of T cell proliferation and T cell antigen receptor signaling by TSP1. A second TSP1 receptor, CD47, was not required for some stimulatory responses to TSP1 but played a significant role in its T cell antigen receptor **antagonist** and antiproliferative activities. Modulating the relative expression or function of these two TSP receptors could therefore alter the direction or magnitude of T cell responses to TSPs.

L10 ANSWER 2 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2

ACCESSION NUMBER: 1996:367205 BIOSIS
DOCUMENT NUMBER: PREV199699089561
TITLE: Metabolism of **thrombospondin 2**: Binding and degradation by 3T3 cells and glycosaminoglycan-variant Chinese hamster ovary cells.
AUTHOR(S): Chen, Hui; Strickland, Dudley K.; Mosher, Deane F. (1)
CORPORATE SOURCE: (1) Dep. Med., Biomol. Chem., Univ. Wisconsin, Madison, 1300 University Ave., Madison, WI 53706 USA
SOURCE: Journal of Biological Chemistry, (1996) Vol. 271, No. 27, pp. 15993-15999.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Thrombospondin 1 (TSP1) and **thrombospondin 2** (TSP2) are members of the thrombospondin family that have a similar structural organization but somewhat different functional activities. Iodinated recombinant mouse TSP2 bound to NIH 3T3 cells and was internalized and degraded through a chloroquine-inhibitable pathway. TSP2 degradation was saturable, specific, and similar to the kinetics of degradation of TSP1. Human platelet TSP1, recombinant mouse TSP1, and recombinant mouse TSP2 cross-competed with one another for degradation by 3T3 cells. Degradation of TSP2 was less sensitive to inhibition by heparin than degradation of TSP1. This is in agreement with differences in heparin-binding affinity of the two TSPs. Degradation of TSP2 was slower in cultures of Chinese

hamster ovary (CHO) cells lacking heparan sulfate proteoglycans than in wild type CHO cells or in cultures of 3T3 cells treated with heparitinase than in untreated 3T3 cells. Degradation of TSP2 was inhibited by antibodies against the low density lipoprotein receptor-related protein (LRP) or by the 39-kDa receptor-associated protein, a known **antagonist** of LRP. This study indicates that TSP2 and TSP1 are metabolized by a common internalization and degradation pathway involving heparan sulfate proteoglycan and LRP. Competition for this pathway is a possible mechanism whereby cells can control the levels and ratio of TSP1 and TSP2 in the extracellular milieu.

L10 ANSWER 3 OF 10 MEDLINE
ACCESSION NUMBER: 2002355447 MEDLINE
DOCUMENT NUMBER: 22001419 PubMed ID: 12006620
TITLE: Trimeric assembly of the C-terminal region of thrombospondin-1 or **thrombospondin-2** is necessary for cell spreading and fascin spike organisation.
AUTHOR: Anilkumar Narayanapanicker; Annis Douglas S; Mosher Deane F; Adams Josephine C
CORPORATE SOURCE: MRC Laboratory for Molecular Cell Biology and Department of Biochemistry and Molecular Biology, University College London, London, WC1E 6BT, UK.
CONTRACT NUMBER: HL54462 (NHLBI)
SOURCE: JOURNAL OF CELL SCIENCE, (2002 Jun 1) 115 (Pt 11) 2357-66. Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20020709
Last Updated on STN: 20021217
Entered Medline: 20021203

AB Thrombospondin-1 (TSP-1) and the highly related protein **thrombospondin-2** (TSP-2) are trimeric extracellular molecules that have complex roles in wound healing, angiogenesis and matrix organisation. At the cellular level, TSP-1 supports cell adhesion and migration by the organisation of fascin spike cytoskeletal structures. To define the molecular requirements for assembly of fascin spikes by thrombospondins, we developed a panel of recombinant protein units of TSP-1 and TSP-2; these were designed according to the domain boundaries and included matched monomeric and trimeric units. These proteins were tested for their effects on cell attachment and fascin spike organisation using C2C12 skeletal myoblasts and vascular smooth muscle cells. In monomeric units, cell attachment activity was localised to the type 1 repeats or type 3 repeats/C-terminal globule, and both regions need to be present in the same molecule for maximal activity. On a molar basis, cell-attachment activities with monomeric units were low compared with intact TSP-1, and no monomeric unit induced cell spreading. Trimeric versions of the type 1 repeats were more adhesive but did not induce cell spreading. Strikingly, trimers that contained the type 3 repeats/C-terminal globule of either TSP-1 or TSP-2 supported cell spreading and fascin spike organisation, producing a similar activity to intact TSP-1. We conclude that trimeric assembly of the highly conserved TSP C-terminal region is necessary for organisation of the fascin-based cytoskeletal structures that are needed for thrombospondin-induced cell motility.

L10 ANSWER 4 OF 10 MEDLINE
ACCESSION NUMBER: 2001516232 MEDLINE
DOCUMENT NUMBER: 21447758 PubMed ID: 11563036
TITLE: Antisense oligonucleotide ISIS 2922 targets IE-expression and prevents HCMV-IE-induced suppression of TSP-1 and TSP-2 expression.

AUTHOR: Margraf S; Bittoova M; Vogel J U; Kotchekov R; Doerr H W; Cinatl J Jr
CORPORATE SOURCE: J. W. Goethe University Hospital, Inst. f. Med. Virology, Paul Ehrlich-Str. 40, D-60596 Frankfurt am Main, Germany.
SOURCE: NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, (2001 Apr-Jul) 20 (4-7) 1425-8.
Journal code: 100892832. ISSN: 1525-7770.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010924
Last Updated on STN: 20020125
Entered Medline: 20020109

AB ISIS 2922, but not ganciclovir (GCV), inhibits HCMV immediate early protein (IE) expression in different infected cell lines and prevents down-modulation of extracellular matrix proteins thrombospondin-1 and -2 induced by IE proteins. While action of ISIS 2922 is mainly due to specific inhibition of IE 2 mRNA, there is also evidence for unspecific effects in terms of inhibition of virus adhesion and penetration.

L10 ANSWER 5 OF 10 MEDLINE
ACCESSION NUMBER: 2001027438 MEDLINE
DOCUMENT NUMBER: 20493603 PubMed ID: 10900205
TITLE: Thrombospondin type 1 repeats interact with matrix metalloproteinase 2. Regulation of metalloproteinase activity.
AUTHOR: Bein K; Simons M
CORPORATE SOURCE: Angiogenesis Research Center, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02215, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 13) 275 (41) 32167-73.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001113

AB Thrombospondins are thought to function as inhibitors of angiogenesis. However, the mechanism(s) of this activity is not well understood. In this study, we have used the yeast two-hybrid system to identify proteins that interact with the thrombospondins 1 (TSP1) and 2 (TSP2) properdin-like type 1 repeats (TSR). One of the proteins identified that interacted with both TSR was matrix metalloproteinase 2 (MMP2). The isolated MMP2 cDNA clone encoded amino acid residues 237-633, which include the fibronectin-like gelatin binding region flanking the catalytic center and the carboxyl hemopexin-like region. Further testing of this clone demonstrated that the TSR interacted with the NH(2)-terminal region of the MMP2 that contains the catalytic domain. The protein interaction observed in yeast was further demonstrated by immunoprecipitation and Western blotting using purified intact TSP1, TSP2, MMP2, and MMP9. Although MMP2 interacted with TSP1 and TSP2 via its gelatin-binding domain or a closely mapping site, neither TSP1 nor TSP2 was degraded by MMP2 in vitro. Tissue culture and in vitro assays demonstrated that the presence of purified TSR and intact TSP1 resulted in inhibition of MMP activity. The ability of TSP1 to inhibit MMP3-dependent activation of pro-MMP9 and thrombin-induced activation of pro-MMP2 suggests that the TSPs may inhibit MMP activity by preventing activation of the MMP2 and MMP9 zymogens.

L10 ANSWER 6 OF 10 MEDLINE
ACCESSION NUMBER: 95212456 MEDLINE
DOCUMENT NUMBER: 95212456 PubMed ID: 7698241
TITLE: Transforming growth factors beta stimulate both thrombospondin-1 and CISP/**thrombospondin-2** synthesis by bovine adrenocortical cells.
AUTHOR: Negoescu A; Lafeuillade B; Pellerin S; Chambaz E M; Feige J J
CORPORATE SOURCE: INSERM Unite 244, CEA, Departement de Biologie Moleculaire et Structurale, Grenoble, France.
SOURCE: EXPERIMENTAL CELL RESEARCH, (1995 Apr) 217 (2) 404-9.
Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950510
Last Updated on STN: 19980206
Entered Medline: 19950428

AB We recently observed that adrenocortical cells secrete, under ACTH treatment, a large trimeric glycoprotein (CISP) presenting amino acid sequence similarity with **thrombospondin-2**. We also observed that the same cells synthesize and secrete thrombospondin-1 whereas under smaller amounts. The aim of this study was to investigate the regulation of these two secreted proteins by members of the TGF beta family of regulatory peptides. We developed an appropriate immunoprecipitation technique that allowed us to quantitate synthesis of thrombospondin-1 and CISP/**thrombospondin-2** in a single assay. Using this assay, we observed that thrombospondin-1 and CISP/**thrombospondin-2** syntheses were respectively stimulated threefold and twofold by a 24-h treatment with 2 ng/ml TGF beta 1. These inductions were dose-dependent (half-maximal effect: 0.2 ng/ml) and time-dependent (detectable after 5 h and plateauing between 15 and 25 h of treatment). They were not observed when transcription was blocked by RNA polymerase inhibitors such as 5,6-dichlorobenzimidazole riboside or actinomycin D. Among members of the TGF beta family, TGF beta 1 and TGF beta 2 and to a lesser extent activin could stimulate thrombospondin-1 and CISP/**thrombospondin-2** synthesis, whereas inhibin and Mullerian inhibiting substance were inactive. Taken together, these data represent the first study on the regulation of both thrombospondin-1 and CISP/**thrombospondin-2** by TGF betas. They further support the concept that TGF beta is a local regulator of adrenocortical functions.

L10 ANSWER 7 OF 10 MEDLINE
ACCESSION NUMBER: 93216653 MEDLINE
DOCUMENT NUMBER: 93216653 PubMed ID: 8463250
TITLE: Thrombospondin is a tight-binding competitive inhibitor of neutrophil elastase.
AUTHOR: Hogg P J; Owensby D A; Mosher D F; Misenheimer T M; Chesterman C N
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, Prince of Wales Hospital, University of New South Wales, Sydney, Australia.
CONTRACT NUMBER: HL29586 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Apr 5) 268 (10) 7139-46.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199305

ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 20000303
Entered Medline: 19930505

AB Thrombospondin, a glycoprotein of three identical disulfide-bonded subunits, is a constituent of platelet alpha-granules and a variety of normal and transformed cells and binds to cell surfaces and becomes incorporated into extracellular matrix. It has been implicated in processes such as wound healing and tumor growth and metastasis. In addition, thrombospondin was shown recently to be an inhibitor of the fibrinolytic enzyme, plasmin. In the cause of studying the effects of thrombospondin on other serine proteinases, we found that thrombospondin binds neutrophil elastase in an active-site-dependent manner and competitively inhibits the activity of the enzyme. In a competitive binding assay, neutrophil elastase bound to thrombospondin with a dissociation constant of 17 +/- 7 nM, expressed per mole of thrombospondin trimer, or 52 +/- 20 nM, expressed per mole of thrombospondin subunit. In kinetic studies of the inhibition of the amidolytic activity of neutrophil elastase by **thrombospondin**, 2.7 +/- 0.3 mol of elastase interacted with 1 mol of thrombospondin trimer with a site-binding constant of 57 +/- 13 nM. Lower limits for the on rate constant of 5 x 10(6) M-1 s-1 and off rate constant of 0.27 s-1 were established. Affinity of binding of neutrophil elastase to thrombospondin was sensitive to ionic strength and calcium ions. Thrombospondin was cleaved by neutrophil elastase, but the site(s) of the limited cleavage are independent of the competitive inhibition of elastase activity by thrombospondin. Neutrophil elastase inactivated with phenylmethylsulfonyl fluoride did not compete with active elastase for binding to thrombospondin, implying that a functional active site is important for the interaction of elastase with thrombospondin. Thrombospondin protected fibronectin from cleavage by neutrophil elastase. In summary, the binding of neutrophil elastase to thrombospondin is tight, reversible, and close enough to the active site of elastase to exclude small synthetic tripeptidyl p-nitroanilide substrates and macromolecular protein substrates. Two potential reactive centers that may be involved in binding elastase have been identified in the calcium-binding type 3 domains of thrombospondin. Neutrophil elastase is the enzyme primarily responsible for degrading and solubilizing connective tissue during inflammatory processes. These findings suggest a previously unsuspected mechanism for regulation of elastase activity at inflammatory sites.

L10 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107136 CAPLUS
DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the wound response by **thrombospondin 2** or osteopontin
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009735	A2	20020207	WO 2001-US24147	20010731
WO 2002009735	A3	20021003		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,

UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002048577 A1 20020425 US 2001-919770 20010731
PRIORITY APPLN. INFO.: US 2000-222071P P 20000801

AB The invention provides methods of modulating the amt. and/or biol. activity of **thrombospondin 2** or osteopontin in an animal. The methods comprise the step of introducing into the animal an amt. of osteopontin, and/or a **thrombospondin** (2) **antagonist**, effective to modulate the amt. or biol. activity of **thrombospondin** (2) or osteopontin in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amt. of an agents or **antagonist** of a matricellular protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or implanted within, the soft tissue of an animal.

L10 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:57331 CAPLUS
DOCUMENT NUMBER: 136:319540
TITLE: Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells
AUTHOR(S): Galon, Jerome; Franchimont, Denis; Hiroi, Naoki; Frey, Gregory; Boettner, Antje; Ehrhart-Bornstein, Monika; O'Shea, John J.; Chrousos, George P.; Bornstein, Stefan R.
CORPORATE SOURCE: Lymphocyte Cell Biology Section, NIAMS, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: FASEB Journal (2002), 16(1), 61-71
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glucocorticoids continue to be the major immunomodulatory agents used in clin. medicine today. However, their actions as anti-inflammatory and immunosuppressive drugs are both beneficial and deleterious. We analyzed the effect of glucocorticoids on the gene expression profile of peripheral blood mononuclear cells from healthy donors. DNA microarray anal. combined with quant. TaqMan PCR and flow cytometry revealed that glucocorticoids induced the expression of chemokine, cytokine, and complement family members as well as of newly discovered innate immune-related genes, including scavenger and Toll-like receptors. In contrast, glucocorticoids repressed the expression of adaptive immune-related genes. Simultaneous inhibitory and stimulatory effects of glucocorticoids were found on inflammatory T helper subsets and apoptosis-related gene clusters. In cells activated by T cell receptor crosslinking, glucocorticoids down-regulated the expression of specific genes that were previously up-regulated in resting cells, suggesting a potential new mechanism by which they exert pos. and neg. effects. Considering the broad and continuously renewed interest in glucocorticoid therapy, the profiles we describe here will be useful in designing more specific and efficient treatment strategies.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:338762 CAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer

PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
WO 2001032928	A3	20020725		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes assocd. with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

L12 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2002:203003 BIOSIS
DOCUMENT NUMBER: PREV200200203003
TITLE: pH-sensitive polymers that enhance intracellular drug delivery in vivo.
AUTHOR(S): Kyriakides, Themis R.; Cheung, Charles Y.; Murthy, Niren; Bornstein, Paul; Stayton, Patrick S.; Hoffman, Allan S. (1)
CORPORATE SOURCE: (1) Department of Bioengineering, University of Washington, Seattle, WA, 98195: hoffman@u.washington.edu USA
SOURCE: Journal of Controlled Release, (17 January, 2002) Vol. 78, No. 1-3, pp. 295-303. http://www.elsevier.com/locate/jconre
1. print.
ISSN: 0168-3659.
DOCUMENT TYPE: Article
LANGUAGE: English

NOT ART APPLICANT!

AB Cytosolic delivery from endosomes is critical for those drugs that are susceptible to attack by lysosomal enzymes, such as DNA, RNA, oligonucleotides, proteins and peptides. Therefore, we have designed pH-sensitive, membrane-disruptive polymers to enhance the release of drugs from the acidic endosomal compartment to the cytoplasm. We have found that one polymer in particular, poly(propylacrylic acid) (PPAA), is very effective at membrane disruption at pHs below 6.5, based on hemolysis studies. PPAA also significantly enhances in vitro transfections of lipoplex formulations in cell culture, and does so in the presence of as much as 50% serum. In this study, we have extended our in vitro hemolysis and cell culture studies to an in vivo murine excisional wound healing model. A pilot study with a green fluorescent protein (GFP)-encoding plasmid indicated that injection of formulations containing PPAA into healing wounds resulted in increased GFP expression. Subsequently, by administering sense and **antisense** DNA for the angiogenesis inhibitor **thrombospondin-2** (TSP2), we were able to alter the wound healing response in TSP2-null and wild type mice, respectively. Our findings showed that when PPAA was added to lipoplex formulations, expression of TSP2 was enhanced in TSP2-null mice compared to control formulations. These results show that PPAA can enhance in vivo transfections and that inhibition of TSP2 expression may lead to improved wound healing. These results suggest that PPAA can provide significant improvements in the in vivo efficacy of drugs such as DNA.

L12 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2000:441929 BIOSIS
DOCUMENT NUMBER: PREV200000441929
TITLE: Cytomegalovirus infection decreases expression of thrombospondin-1 and -2 in cultured human retinal glial cells: Effects of antiviral agents.
AUTHOR(S): Cinatl, Jindrich, Jr. (1); Bittoova, Martina; Margraf, Stefan; Vogel, Jens-Uwe; Cinatl, Jaroslav; Preiser, Wolfgang; Doerr, Hans Wilhelm
CORPORATE SOURCE: (1) Zentrum der Hygiene, Institut fuer Medizinische Virologie, Klinikum der Johann Wolfgang Goethe-Universitaet, Paul-Ehrlich Str. 40, D-60596, Frankfurt am Main Germany
SOURCE: Journal of Infectious Diseases, (September, 2000) Vol. 182, No. 3, pp. 643-651. print.
ISSN: 0022-1899.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In fibroblasts, infection with human cytomegalovirus (HCMV) inhibits expression of the extracellular matrix proteins thrombospondin-1 and -2 (TSP-1 and TSP-2). These effects may depend on expression of HCMV immediate-early (IE) genes, which are activated by cellular transcription factor NF-kappaB. The influence of HCMV infection on TSP-1 and TSP-2 expression and the ability of different antiviral drugs to prevent these

cellular changes in permissive cultures of human retinal glial cells were observed. Ganciclovir inhibited only HCMV late antigen (LA) expression, whereas **antisense** oligonucleotide ISIS 2922 and peptide SN50, inhibitors of HCMV IE expression and NF-kappaB activity, respectively, inhibited both IE and LA expression. ISIS 2922 and SN50, but not ganciclovir, prevented down-modulation of TSP-1 and TSP-2. The results showed that HCMV-induced down-modulation of TSP-1 and TSP-2 in retinal glial cells is prevented by inhibition of HCMV IE expression. These findings may be relevant to pathogenesis and treatment of HCMV retinitis.

L12 ANSWER 3 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001345688 MEDLINE
DOCUMENT NUMBER: 21301855 PubMed ID: 11407897
TITLE: Regulation of angiogenesis and matrix remodeling by localized, matrix-mediated **antisense** gene delivery.
AUTHOR: Kyriakides T R; Hartzel T; Huynh G; Bornstein P
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, Washington 98195, USA.
CONTRACT NUMBER: AR45418 (NIAMS)
HL18645 (NHLBI)
SOURCE: MOLECULAR THERAPY, (2001 Jun) 3 (6) 842-9.
Journal code: 100890581. ISSN: 1525-0016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010903
Last Updated on STN: 20010903
Entered Medline: 20010830

NOT ARE APPLICANTS!

AB Implantation of biomaterials, such as glucose sensors, leads to the formation of a poorly vascularized collagenous capsule that can lead to implant failure. This process, known as the foreign body reaction (FBR), develops in response to almost all biomaterials and consists of overlapping phases similar to those in wound healing. Implantation of porous biomaterials, such as polyvinyl alcohol sponges, also leads to granuloma formation within the interstices of the sponge prior to encapsulation by the FBR. We asked whether delivery of an **antisense** cDNA for the potent angiogenesis inhibitor thrombospondin (TSP) 2 would enhance blood vessel formation and alter collagen fibrillogenesis in the sponge granuloma and capsule. Collagen solutions were mixed with plasmid to generate gene-activated matrices (GAMs) and applied to biomaterials that were then implanted subcutaneously. Sustained expression of plasmid-encoded proteins was observed at 2 weeks and a month following implantation. In vivo delivery of plasmids, encoding either sense or **antisense** TSP2 cDNA, altered blood vessel formation and collagen deposition in TSP2-null and wild-type mice, respectively. Untreated implants, implanted next to GAM-treated implants, did not show exogenous gene expression and did not elicit altered responses, suggesting that gene delivery was limited to implant sites. This method of **antisense** DNA delivery has the potential to improve the performance and life span of implantable delivery devices and biosensors.

L12 ANSWER 4 OF 6 MEDLINE
ACCESSION NUMBER: 2001350395 MEDLINE
DOCUMENT NUMBER: 21280787 PubMed ID: 11387198
TITLE: **Thrombospondin-2** plays a protective role in multistep carcinogenesis: a novel host anti-tumor defense mechanism.
AUTHOR: Hawighorst T; Velasco P; Streit M; Hong Y K; Kyriakides T R; Brown L F; Bornstein P; Detmar M
CORPORATE SOURCE: Cutaneous Biology Research Center and Department of

Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA.

CONTRACT NUMBER: AR45418 (NIAMS)
CA69184 (NCI)
CA86410 (NCI)
HL18645 (NHLBI)

SOURCE: EMBO JOURNAL, (2001 Jun 1) 20 (11) 2631-40.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB The angiogenic switch during tumorigenesis is thought to be induced by a change in the balance of pro- angiogenic and anti-angiogenic factors. To elucidate the biological role of the endogenous angiogenesis inhibitor **thrombospondin-2** (TSP-2) during multistep carcinogenesis, we subjected TSP-2-deficient and wild-type mice to a chemical skin carcinogenesis regimen. Surprisingly, TSP-2 expression was strongly upregulated in the mesenchymal stroma of wild-type mice throughout the consecutive stages of tumorigenesis whereas the angiogenesis factor, vascular endothelial growth factor, was induced predominantly in tumor cells. TSP-2 deficiency dramatically enhanced susceptibility to skin carcinogenesis and resulted in accelerated and increased tumor formation. The angiogenic switch occurred in early stages of pre-malignant tumor formation, and tumor angiogenesis was significantly enhanced in TSP-2-deficient mice. While TSP-2 deficiency did not affect tumor differentiation or proliferation, tumor cell apoptosis was significantly reduced. These results reveal upregulation of an endogenous angiogenesis inhibitor during multi step tumorigenesis and identify enhanced stromal TSP-2 expression as a novel host anti-tumor defense mechanism.

L12 ANSWER 5 OF 6 MEDLINE

ACCESSION NUMBER: 2001516232 MEDLINE
DOCUMENT NUMBER: 21447758 PubMed ID: 11563036

TITLE: **Antisense** oligonucleotide ISIS 2922 targets IE-expression and prevents HCMV-IE-induced suppression of TSP-1 and TSP-2 expression.

AUTHOR: Margraf S; Bittoova M; Vogel J U; Kotchekov R; Doerr H W; Cinatl J Jr
CORPORATE SOURCE: J. W. Goethe University Hospital, Inst. f. Med. Virology, Paul Ehrlich-Str. 40, D-60596 Frankfurt am Main, Germany.

SOURCE: NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, (2001 Apr-Jul) 20 (4-7) 1425-8.
Journal code: 100892832. ISSN: 1525-7770.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010924
Last Updated on STN: 20020125
Entered Medline: 20020109

AB ISIS 2922, but not ganciclovir (GCV), inhibits HCMV immediate early protein (IE) expression in different infected cell lines and prevents down-modulation of extracellular matrix proteins thrombospondin-1 and -2 induced by IE proteins. While action of ISIS 2922 is mainly due to specific inhibition of IE 2 mRNA, there is also evidence for unspecific effects in terms of inhibition of virus adhesion and penetration.

L12 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107136 CAPLUS
DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the wound response by **thrombospondin 2** or osteopontin
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009735	A2	20020207	WO 2001-US24147	20010731
WO 2002009735	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002048577	A1	20020425	US 2001-919770	20010731

PRIORITY APPLN. INFO.: US 2000-222071P P 20000801

AB The invention provides methods of modulating the amt. and/or biol. activity of **thrombospondin 2** or osteopontin in an animal. The methods comprise the step of introducing into the animal an amt. of osteopontin, and/or a **thrombospondin** (2) antagonist, effective to modulate the amt. or biol. activity of **thrombospondin** (2) or osteopontin in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amt. of an agents or antagonist of a matricellular protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or implanted within, the soft tissue of an animal.

L13 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107136 CAPLUS
DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the wound response by **thrombospondin 2** or osteopontin
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009735	A2	20020207	WO 2001-US24147	20010731
WO 2002009735	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002048577	A1	20020425	US 2001-919770	20010731

PRIORITY APPLN. INFO.: US 2000-222071P P 20000801

AB The invention provides methods of modulating the amt. and/or biol. activity of **thrombospondin 2** or osteopontin in an animal. The methods comprise the step of introducing into the animal an amt. of osteopontin, and/or a **thrombospondin** (2) antagonist, effective to modulate the amt. or biol. activity of **thrombospondin** (2) or osteopontin in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amt. of an agents or antagonist of a matricellular protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or implanted within, the soft tissue of an animal.

L16 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2002:363702 BIOSIS
DOCUMENT NUMBER: PREV200200363702
TITLE: Interactions of thrombospondins with alpha4beta1 integrin and CD47 differentially modulate T cell behavior.
AUTHOR(S): Li, Zhuqing; Calzada, Maria J.; Sipes, John M.; Cashel, Jo Anne; Krutzsch, Henry C.; Annis, Douglas S.; Mosher, Deane F.; Roberts, David D. (1)
CORPORATE SOURCE: (1) National Institutes of Health, 10 Center Dr., Building 10, Room 2A33, MSC 1500, Bethesda, MD, 20892-1500: droberts@helix.nih.gov USA
SOURCE: Journal of Cell Biology, (April 29, 2002) Vol. 157, No. 3, pp. 509-519. http://www.jcb.org/. print.
ISSN: 0021-9525.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Thrombospondin (TSP)-1 has been reported to modulate T cell behavior both positively and negatively. We found that these opposing responses arise from interactions of TSP1 with two different T cell receptors. The integrin alpha4beta1 recognizes an LDVP sequence in the NH2-terminal domain of TSP1 and was required for stimulation of T cell adhesion, chemotaxis, and matrix metalloproteinase gene expression by TSP1. Recognition of TSP1 by T cells depended on the activation state of alpha4beta1 integrin, and TSP1 inhibited interaction of activated alpha4beta1 integrin on T cells with its counter receptor vascular cell adhesion molecule-1. The alpha4beta1 integrin recognition site is conserved in **TSP2**. A recombinant piece of **TSP2** containing this sequence replicated the alpha4beta1 integrin-dependent activities of TSP1. The beta1 integrin recognition sites in TSP1, however, were neither necessary nor sufficient for inhibition of T cell proliferation and T cell antigen receptor signaling by TSP1. A second TSP1 receptor, CD47, was not required for some stimulatory responses to TSP1 but played a significant role in its T cell antigen receptor **antagonist** and antiproliferative activities. Modulating the relative expression or function of these two TSP receptors could therefore alter the direction or magnitude of T cell responses to TSPs.

L16 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 1996:367205 BIOSIS
DOCUMENT NUMBER: PREV199699089561
TITLE: Metabolism of thrombospondin 2: Binding and degradation by 3T3 cells and glycosaminoglycan-variant Chinese hamster ovary cells.
AUTHOR(S): Chen, Hui; Strickland, Dudley K.; Mosher, Deane F. (1)
CORPORATE SOURCE: (1) Dep. Med., Biomol. Chem., Univ. Wisconsin, Madison, 1300 University Ave., Madison, WI 53706 USA
SOURCE: Journal of Biological Chemistry, (1996) Vol. 271, No. 27, pp. 15993-15999.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Thrombospondin 1 (TSP1) and thrombospondin 2 (**TSP2**) are members of the thrombospondin family that have a similar structural organization but somewhat different functional activities. Iodinated recombinant mouse **TSP2** bound to NIH 3T3 cells and was internalized and degraded through a chloroquine-inhibitable pathway. **TSP2** degradation was saturable, specific, and similar to the kinetics of degradation of TSP1. Human platelet TSP1, recombinant mouse TSP1, and recombinant mouse **TSP2** cross-competed with one another for degradation by 3T3 cells. Degradation of **TSP2** was less sensitive to inhibition by heparin than degradation of TSP1. This is in agreement with differences in heparin-binding affinity of the two TSPs. Degradation of **TSP2** was slower in cultures of Chinese hamster ovary (CHO) cells lacking heparan sulfate proteoglycans than in wild type CHO cells or in cultures

of 3T3 cells treated with heparitinase than in untreated 3T3 cells. Degradation of **TSP2** was inhibited by antibodies against the low density lipoprotein receptor-related protein (LRP) or by the 39-kDa receptor-associated protein, a known **antagonist** of LRP. This study indicates that **TSP2** and TSP1 are metabolized by a common internalization and degradation pathway involving heparan sulfate proteoglycan and LRP. Competition for this pathway is a possible mechanism whereby cells can control the levels and ratio of TSP1 and **TSP2** in the extracellular milieu.

L16 ANSWER 3 OF 4 MEDLINE
ACCESSION NUMBER: 2001027438 MEDLINE
DOCUMENT NUMBER: 20493603 PubMed ID: 10900205
TITLE: Thrombospondin type 1 repeats interact with matrix metalloproteinase 2. Regulation of metalloproteinase activity.
AUTHOR: Bein K; Simons M
CORPORATE SOURCE: Angiogenesis Research Center, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02215, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 13) 275 (41) 32167-73.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001113

AB Thrombospondins are thought to function as inhibitors of angiogenesis. However, the mechanism(s) of this activity is not well understood. In this study, we have used the yeast two-hybrid system to identify proteins that interact with the thrombospondins 1 (TSP1) and 2 (**TSP2**) properdin-like type 1 repeats (TSR). One of the proteins identified that interacted with both TSR was matrix metalloproteinase 2 (MMP2). The isolated MMP2 cDNA clone encoded amino acid residues 237-633, which include the fibronectin-like gelatin binding region flanking the catalytic center and the carboxyl hemopexin-like region. Further testing of this clone demonstrated that the TSR interacted with the NH(2)-terminal region of the MMP2 that contains the catalytic domain. The protein interaction observed in yeast was further demonstrated by immunoprecipitation and Western blotting using purified intact TSP1, **TSP2**, MMP2, and MMP9. Although MMP2 interacted with TSP1 and **TSP2** via its gelatin-binding domain or a closely mapping site, neither TSP1 nor **TSP2** was degraded by MMP2 in vitro. Tissue culture and in vitro assays demonstrated that the presence of purified TSR and intact TSP1 resulted in inhibition of MMP activity. The ability of TSP1 to inhibit MMP3-dependent activation of pro-MMP9 and thrombin-induced activation of pro-MMP2 suggests that the TSPs may inhibit MMP activity by preventing activation of the MMP2 and MMP9 zymogens.

L16 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107136 CAPLUS
DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the wound response by thrombospondin 2 or osteopontin
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009735	A2	20020207	WO 2001-US24147	20010731
WO 2002009735	A3	20021003		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002048577	A1	20020425	US 2001-919770	20010731

PRIORITY APPLN. INFO.: US 2000-222071P P 20000801

AB The invention provides methods of modulating the amt. and/or biol. activity of thrombospondin 2 or osteopontin in an animal. The methods comprise the step of introducing into the animal an amt. of osteopontin, and/or a thrombospondin (2) **antagonist**, effective to modulate the amt. or biol. activity of thrombospondin (2) or osteopontin in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amt. of an agents or **antagonist** of a matricellular protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or implanted within, the soft tissue of an animal.

L18 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2002:203003 BIOSIS
DOCUMENT NUMBER: PREV200200203003
TITLE: pH-sensitive polymers that enhance intracellular drug delivery in vivo.
AUTHOR(S): Kyriakides, Themis R.; Cheung, Charles Y.; Murthy, Niren; Bornstein, Paul; Stayton, Patrick S.; Hoffman, Allan S. (1)
CORPORATE SOURCE: (1) Department of Bioengineering, University of Washington, Seattle, WA, 98195: hoffman@u.washington.edu USA
SOURCE: Journal of Controlled Release, (17 January, 2002) Vol. 78, No. 1-3, pp. 295-303. http://www.elsevier.com/locate/jconrel. print.
ISSN: 0168-3659.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Cytosolic delivery from endosomes is critical for those drugs that are susceptible to attack by lysosomal enzymes, such as DNA, RNA, oligonucleotides, proteins and peptides. Therefore, we have designed pH-sensitive, membrane-disruptive polymers to enhance the release of drugs from the acidic endosomal compartment to the cytoplasm. We have found that one polymer in particular, poly(propylacrylic acid) (PPAA), is very effective at membrane disruption at pHs below 6.5, based on hemolysis studies. PPAA also significantly enhances in vitro transfections of lipoplex formulations in cell culture, and does so in the presence of as much as 50% serum. In this study, we have extended our in vitro hemolysis and cell culture studies to an in vivo murine excisional wound healing model. A pilot study with a green fluorescent protein (GFP)-encoding plasmid indicated that injection of formulations containing PPAA into healing wounds resulted in increased GFP expression. Subsequently, by administering sense and **antisense** DNA for the angiogenesis inhibitor thrombospondin-2 (**TSP2**), we were able to alter the wound healing response in **TSP2**-null and wild type mice, respectively. Our findings showed that when PPAA was added to lipoplex formulations, expression of **TSP2** was enhanced in **TSP2** -null mice compared to control formulations. These results show that PPAA can enhance in vivo transfections and that inhibition of **TSP2** expression may lead to improved wound healing. These results suggest that PPAA can provide significant improvements in the in vivo efficacy of drugs such as DNA.

L18 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 1994:485385 BIOSIS
DOCUMENT NUMBER: PREV199497498385
TITLE: Tissue factor controls the balance of angiogenic and antiangiogenic properties of tumor cells in mice.
AUTHOR(S): Zhang, Youming; Deng, Youhua; Luther, Thomas; Mueler, Martin; Ziegler, Reinhard; Waldherr, Ruediger; Stern, David Mark; Nawroth, Peter Paul (1)
CORPORATE SOURCE: (1) Univ. Heidelberg, Dep. Med. I, Bergheimer Strasse 58, D 69115 Heidelberg Germany
SOURCE: Journal of Clinical Investigation, (1994) Vol. 94, No. 3, pp. 1320-1327.
ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Meth-A sarcoma cells were stable transfected to overexpress (sense construct) or underexpress (**antisense** construct) tissue factor. In vitro, there was no difference in plating efficiency or growth between these cell lines, in vivo, tumor cells transfected to overexpress tissue factor grew more rapidly, and established larger and more vascularized tumors than control transfectants. **Antisense** transfectants grew the slowest and were the least vascularized. Anticoagulation of mice with warfarin did not alter the difference between these tumor lines. Tumor cells overexpressing tissue factor released more (compared with control

transfectants) mitogenic activity for endothelial cells in parallel with enhanced transcription of vascular permeability factor/vascular endothelial cell growth factor (VEGF/VPF), and diminished transcription of thrombospondin (**TSP2**), a molecule with anti-angiogenic properties. **Antisense** tissue factor transfectants, while releasing the lowest amount of mitogenic activity, had increased thrombospondin and decreased VEGF/VPF transcription compared with control transfectants or wild-type cells. Experiments with these sense, **antisense**, truncated sense, or vector tumor lines gave comparable results in complete medium, serum free medium or in the presence of hirudin, indicating that the activation of the coagulation mechanism was not likely to be responsible for changes in tumor cell properties. These results suggest that tissue factor regulates angiogenic properties of tumor cells by altering the production of growth regulatory molecules of endothelium by a mechanism distinct from tissue factor activation of the coagulation mechanism.

L18 ANSWER 3 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001345688 MEDLINE
DOCUMENT NUMBER: 21301855 PubMed ID: 11407897
TITLE: Regulation of angiogenesis and matrix remodeling by localized, matrix-mediated **antisense** gene delivery.
AUTHOR: Kyriakides T R; Hartzel T; Huynh G; Bornstein P
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, Washington 98195, USA.
CONTRACT NUMBER: AR45418 (NIAMS)
HL18645 (NHLBI)
SOURCE: MOLECULAR THERAPY, (2001 Jun) 3 (6) 842-9.
Journal code: 100890581. ISSN: 1525-0016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010903
Last Updated on STN: 20010903
Entered Medline: 20010830

AB Implantation of biomaterials, such as glucose sensors, leads to the formation of a poorly vascularized collagenous capsule that can lead to implant failure. This process, known as the foreign body reaction (FBR), develops in response to almost all biomaterials and consists of overlapping phases similar to those in wound healing. Implantation of porous biomaterials, such as polyvinyl alcohol sponges, also leads to granuloma formation within the interstices of the sponge prior to encapsulation by the FBR. We asked whether delivery of an **antisense** cDNA for the potent angiogenesis inhibitor thrombospondin (TSP) 2 would enhance blood vessel formation and alter collagen fibrillogenesis in the sponge granuloma and capsule. Collagen solutions were mixed with plasmid to generate gene-activated matrices (GAMs) and applied to biomaterials that were then implanted subcutaneously. Sustained expression of plasmid-encoded proteins was observed at 2 weeks and a month following implantation. In vivo delivery of plasmids, encoding either sense or **antisense TSP2** cDNA, altered blood vessel formation and collagen deposition in **TSP2**-null and wild-type mice, respectively. Untreated implants, implanted next to GAM-treated implants, did not show exogenous gene expression and did not elicit altered responses, suggesting that gene delivery was limited to implant sites. This method of **antisense** DNA delivery has the potential to improve the performance and life span of implantable delivery devices and biosensors.

L18 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107136 CAPLUS

DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the wound response by thrombospondin 2 or osteopontin
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009735	A2	20020207	WO 2001-US24147	20010731
WO 2002009735	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002048577	A1	20020425	US 2001-919770	20010731

PRIORITY APPLN. INFO.: US 2000-222071P P 20000801

AB The invention provides methods of modulating the amt. and/or biol. activity of thrombospondin 2 or osteopontin in an animal. The methods comprise the step of introducing into the animal an amt. of osteopontin, and/or a thrombospondin (2) antagonist, effective to modulate the amt. or biol. activity of thrombospondin (2) or osteopontin in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amt. of an agents or antagonist of a matricellular protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or implanted within, the soft tissue of an animal.

L19 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107136 CAPLUS
DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the wound response by thrombospondin 2 or osteopontin
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009735	A2	20020207	WO 2001-US24147	20010731
WO 2002009735	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002048577	A1	20020425	US 2001-919770	20010731

PRIORITY APPLN. INFO.: US 2000-222071P P 20000801

AB The invention provides methods of modulating the amt. and/or biol. activity of thrombospondin 2 or osteopontin in an animal. The methods comprise the step of introducing into the animal an amt. of osteopontin, and/or a thrombospondin (2) antagonist, effective to modulate the amt. or biol. activity of thrombospondin (2) or osteopontin in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amt. of an agents or antagonist of a matricellular protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or implanted within, the soft tissue of an animal.

L26 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2000:303524 BIOSIS
DOCUMENT NUMBER: PREV200000303524
TITLE: Elastase and matrix metalloproteinase inhibitors induce regression, and tenascin-C antisense prevents progression, of vascular disease.
AUTHOR(S): Cowan, Kyle Northcote; Jones, Peter Lloyd; Rabinovitch, Marlene (1)
CORPORATE SOURCE: (1) Division of Cardiovascular Research, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8 Canada
SOURCE: Journal of Clinical Investigation, (January, 2000) Vol. 105, No. 1, pp. 21-34. print.
ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Increased expression of the glycoprotein tenascin-C (TN) is associated with progression of clinical and experimental pulmonary hypertension. In cultured smooth muscle cells (SMCs) TN is induced by matrix metalloproteinases (MMPs) and amplifies the proliferative response to growth factors. Conversely, suppression of TN leads to SMC apoptosis. We now report that hypertrophied rat pulmonary arteries in organ culture, which progressively thicken in association with cell proliferation and matrix accumulation, can be made to regress by inhibiting either serine elastases or MMPs. This effect is associated with reduced TN, suppression of SMC proliferation, and induction of apoptosis. Selective repression of TN by transfecting pulmonary arteries with antisense/**ribozyme** constructs also induces SMC apoptosis and arrests progressive vascular thickening but fails to induce regression. This failure is related to concomitant expansion of a SMC population, which produces an alternative cell survival alphavbeta3 ligand, **osteopontin** (OPN), in response to pro-proliferative cues provided by a proteolytic environment. OPN rescues MMP inhibitor-induced SMC apoptosis, and alphavbeta3 blockade induces apoptosis in hypertrophied arteries. Our data suggest that proteinase inhibition is a novel strategy to induce regression of vascular disease because this overcomes the pluripotentiality of SMC-matrix survival interactions and induces coordinated apoptosis and resorption of matrix.

L26 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 1995:550855 BIOSIS
DOCUMENT NUMBER: PREV199698565155
TITLE: **Osteopontin** (OPN) may facilitate metastasis by protecting cells from macrophage NO-mediated cytotoxicity: Evidence from cell lines down-regulated for OPN expression by a targeted **ribozyme**.
AUTHOR(S): Feng, Bo; Rollo, Ellen E.; Denhardt, David T. (1)
CORPORATE SOURCE: (1) Nelson Biol. Lab., PO Box 1059, Piscataway, NJ 08855 USA
SOURCE: Clinical & Experimental Metastasis, (1995) Vol. 13, No. 6, pp. 453-462.
ISSN: 0262-0898.
DOCUMENT TYPE: Article
LANGUAGE: English
AB **Osteopontin** (OPN) is a GRGDS-containing phosphoglycoprotein that is capable of facilitating cell adhesion and modulating gene expression via integrin receptors. Three hammerhead **ribozymes** designed to target three different regions of OPN mRNA were shown to cleave the message catalytically in vitro. Plasmid vectors that had been engineered to express the **ribozymes** in mammalian cells were used to generate stably transfected T24 H-ras-transformed NIH3T3 cells that normally express OPN at high levels. Northern and Western blot analyses showed that OPN mRNA and protein expression were reduced in a subset of

these anti-OPN **ribozyme**-expressing cell lines. Cells whose ability to produce OPN had been impaired exhibited greater sensitivity to the cytotoxic action of activated RAW264.7 macrophage-like cells; they were also less effective at suppressing macrophage NO production. In agreement with previous reports, they were also less tumorigenic and metastatic in an experimental metastasis assay. These results are consistent with the hypothesis that OPN serves as a defense against NO-mediated host cell cytotoxicity and thereby augments the metastatic phenotype.

L26 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:432652 BIOSIS
DOCUMENT NUMBER: PREV199900432652
TITLE: **Ribozyme** ablation reveals the molecular identity of the 1,25(OH)2D3-regulated calcium channel in osteoblastic cells.
AUTHOR(S): Liu, R. (1); Farach-Carson, M. C.
CORPORATE SOURCE: (1) Dental Branch, University of Texas-Houston, Houston, TX USA
SOURCE: Journal of Bone and Mineral Research, (Sept., 1999) Vol. 14, No. SUPPL. 1, pp. S211.
Meeting Info.: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research St. Louis, Missouri, USA September 30-October 4, 1999 American Society for Bone and Mineral Research
. ISSN: 0884-0431.
DOCUMENT TYPE: Conference
LANGUAGE: English

L26 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:869204 CAPLUS
DOCUMENT NUMBER: 137:367975
TITLE: Diagnosis of progredient chronic dementia by detection of **osteopontin**-derived markers in body fluids
INVENTOR(S): Lamping, Norbert; Zucht, Hans-Dieter; Heine, Gabriele; Juergens, Michael; Hess, Ruediger; Selle, Hartmut
PATENT ASSIGNEE(S): Biovision A.G., Germany
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002090974	A2	20021114	WO 2002-DE1665	20020508

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 2001-10122543 A 20010509
AB The invention relates to defined peptides and the quant. detn. thereof in body fluids of patients suffering from progredient chronic dementia, in relation to the concn. of said peptides in a control group. The inventive peptides come from a protein precursor that is processed in a specific manner, and that is optionally post-translationally modified, esp.

phosphorylated. Specifically, **osteopontin** is discussed. An increase in the concns. of these peptides or the corresponding non-processed protein indicates progredient chronic dementia. Progredient chronic dementia is detected by identifying the peptides and/or the protein individually or in combinations. The invention also relates to the use of said peptides for controlling the course of progredient chronic dementia and for the prognosis of progredient chronic dementia, esp. for complementing or replacing mini-mental scores, and for developing therapeutic agents to combat progredient chronic dementia such as Alzheimer's disease.

L26 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107136 CAPLUS
DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the wound response by thrombospondin 2 or **osteopontin**
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009735	A2	20020207	WO 2001-US24147	20010731
WO 2002009735	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002048577	A1	20020425	US 2001-919770	20010731

PRIORITY APPLN. INFO.: US 2000-222071P P 20000801

AB The invention provides methods of modulating the amt. and/or biol. activity of thrombospondin 2 or **osteopontin** in an animal. The methods comprise the step of introducing into the animal an amt. of **osteopontin**, and/or a thrombospondin (2) antagonist, effective to modulate the amt. or biol. activity of thrombospondin (2) or **osteopontin** in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amt. of an agents or antagonist of a matricellular protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or implanted within, the soft tissue of an animal.

L26 ANSWER 6 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002054999 EMBASE
TITLE: The metastasis gene **osteopontin**: A candidate target for cancer therapy.
AUTHOR: Weber G.F.
CORPORATE SOURCE: G.F. Weber, Department of Radiation Oncology, New England Medical Center, Tufts University Medical School, 750 Washington Street, Boston, MA 02111, United States. gweber@lifespan.org
SOURCE: Biochimica et Biophysica Acta - Reviews on Cancer, (28 Dec

2001) 1552/2 (61-85).
Refs: 157
ISSN: 0304-419X CODEN: BBACEU
PUBLISHER IDENT.: S 0304-419X(01)00037-3
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Malignant tumors are characterized by dysregulated growth control, overcoming of replicative senescence, and metastasis formation. Current therapeutic regimens mostly exert their effects through inhibition of cell cycle progression, leaving two major components of transformation untouched. The cytokine **osteopontin** is essential for the dissemination of various cancers. Past research has implied several modes in which **osteopontin** and its main receptors on tumor cells can be suppressed. **Osteopontin** expression is inhibitable on the levels of gene transcription and the RNA message, and the **osteopontin** protein can be blocked with antibodies or synthetic peptides. The **osteopontin** receptor CD44 has been targeted by diverse therapeutic strategies, including cytotoxic and immunotherapeutic approaches. The receptor integrin .alpha.(V).beta.(3) contributes not only to tumor cell dissemination, but also to angiogenesis and osteolysis in bone metastases. Small molecule inhibitors of this receptor are under study as drug candidates. Because receptors and cytokine ligands that mediate metastasis formation are sparsely expressed in the adult healthy organism and are more readily reached by pharmaceuticals than intracellular drug targets they may represent a particularly suitable focus for therapeutic intervention. .COPYRGT. 2001 Elsevier Science B.V. All rights reserved.

L26 ANSWER 7 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998102488 EMBASE
TITLE: Mechanisms of angiogenesis in vascular disorders: Potential therapeutic targets.
AUTHOR: Mousa S.A.
CORPORATE SOURCE: S.A. Mousa, DuPont Merck Pharmaceutical Co., Experimental Station, Wilmington, DE 19880-0400, United States
SOURCE: Drugs of the Future, (1998) 23/1 (51-60).
Refs: 16
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Recent evidence suggests that, in spite of the redundancy of angiogenic factors involved in pathological angiogenesis, strategies aimed at inhibiting specific endothelial cell angiogenic factors at their release or receptor level may form the basis for effective and safe treatment of angiogenic- mediated disease processes. Physiologic angiogenesis is fundamental to reproduction, development and repair. Pathological angiogenesis sustains the progression of many neoplastic and proinflammatory diseases. The idea that tumor growth is angiogenesis-dependent was first proposed by Folkman et al. (1). This hypothesis is now supported by extensive experimental evidence from which a wide spectrum of diagnostic and therapeutic applications have been advanced.

L27 ANSWER 1 OF 2 MEDLINE
ACCESSION NUMBER: 2002720319 IN-PROCESS
DOCUMENT NUMBER: 22370267 PubMed ID: 12482823
TITLE: PlA polymorphism of integrin beta3 differentially modulates cellular migration on extracellular matrix proteins.
AUTHOR: Sajid Mansoor; Vijayan K Vinod; Souza Shiloe; Bray Paul F
CORPORATE SOURCE: Department of Medicine, Baylor College of Medicine, Houston, Tex 77030, USA.
SOURCE: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (2002 Dec 1) 22 (12) 1984-9.
Journal code: 9505803. ISSN: 1524-4636.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20021218
Last Updated on STN: 20021218

AB OBJECTIVE: Cell migration is central to multiple physiological and pathologic processes and involves interactions between integrins on the cell surface and the extracellular matrix. The Leu33Pro (PlA) polymorphism of integrin beta3 has been reported to be associated with a greater rate of restenosis after angioplasty, a process involving endothelial and smooth muscle cell migration. We have addressed the possibility that the Leu33Pro polymorphism could modify the migratory behavior of Chinese hamster ovary (CHO) cells expressing the beta3-containing integrin complexes. METHODS AND RESULTS: Haptotactic migratory responses of CHO alpha(IIb)beta3 cells to fibronectin and vitronectin were not statistically different between the Leu33 and Pro33 cells. However, CHO cells with the Pro33 (PlA2) polymorphism had an enhanced haptotactic migratory response to fibrinogen and von Willebrand Factor. This enhanced migration (1) could be blocked by the alpha(IIb)beta3-complex-specific neutralizing mAb 10E5, by 7E3, a neutralizing mAb specific for the beta3 integrin, and by the alpha(IIb)beta3-**blocking peptide** Integrilin; (2) was not observed with a CHO cell line expressing an activating beta3 Cys435 to Ala mutation; and (3) was attributable to increased activity of mitogen-activated protein kinase and cyclooxygenase. CHO cell lines expressing the Pro33 isoform of alpha(v)beta3 had an enhanced haptotactic migratory response to vitronectin and **osteopontin** but not fibrinogen. CONCLUSIONS: The Leu33Pro polymorphism alters the migratory behavior of cells on extracellular matrix substrates, and the alpha subunit influences the substrate specificity of this genetic effect.

L27 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:436 CAPLUS
DOCUMENT NUMBER: 136:145550
TITLE: Attachment of human periodontal ligament cells to enamel matrix-derived protein is mediated via interaction between BSP-like molecules and integrin .alpha.v.beta.3
AUTHOR(S): Suzuki, Naoto; Ohyama, Mariko; Maeno, Masao; Ito, Koichi; Otsuka, Kichibee
CORPORATE SOURCE: Department of Biochemistry, Division of Functional Morphology, Dental Research Center, Nihon University School of Dentistry, Tokyo, Japan
SOURCE: Journal of Periodontology (2001), 72(11), 1520-1526
CODEN: JOPRAJ; ISSN: 0022-3492
PUBLISHER: American Academy of Periodontology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Although enamel matrix-derived protein (EMD) can stimulate attachment of human periodontal ligament (HPDL) cells to the root surface, the biol. mechanism of this phenomenon is unclear. The purpose of this study was to det. which mols. in EMD are involved in the attachment of HPDL cells, and

which types of integrins on the cell surface mediate the interaction between the cells and EMD. HPDL explants were obtained from tooth surfaces extd. from 4 individuals, and cells taken from the individual explants were sep. harvested and subcultured through as many as 5 passages. Cells were incubated on EMD-coated culture plates with and without neutral antibodies for integrins or RGD-sequence **blocking peptides** and stained with toluidine blue. Proteins in EMD that were able to induce cell attachment were identified by incubating SDS-PAGE replicas with HPDL cells; the cell-binding regions were detected by staining the cells with toluidine blue. Characteristics of the cell-binding proteins in the EMD were identified by Western blot anal. It was shown that anti-.alpha.v.beta.3 antibody and GRGDSP peptide markedly reduced attachment of HPDL cells to EMD. When the cells were incubated with SDS-PAGE replicas, distinct cell attachment was obsd. at a mol. mass of approx. 55 kDa. The cell-binding ability of this protein was completely blocked by treatment with anti-.alpha.v.beta.3 antibody or GRGDSP peptide. In the Western blot anal., the 55-kDa protein was recognized by anti-bone sialoprotein (BSP) antibody as a single band. The authors' study provides the first evidence that the attachment of HPDL cells to EMD can be mediated by interaction between a BSP-like mol. and integrin .alpha.v.beta.3 on the cell surface.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 1 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2002:169595 BIOSIS
DOCUMENT NUMBER: PREV200200169595
TITLE: Osteopontin stimulates tumor growth and activation of promatrix metalloproteinase-2 through nuclear factor-kappaB-mediated induction of membrane type 1 matrix metalloproteinase in murine melanoma cells.
AUTHOR(S): Philip, Subha; Bulbule, Anuradha; Kundu, gopal C. (1)
CORPORATE SOURCE: (1) National Center for Cell Science, NCCS Complex, Pune, 411 007: gopalkundu@hotmail.com India
SOURCE: Journal of Biological Chemistry, (November 30, 2001) Vol. 276, No. 48, pp. 44926-44935. http://www.jbc.org/. print. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Matrix metalloproteinase (MMPs) degrade the extra-cellular matrix (ECM) and play critical roles in tissue repairs, tumor invasion, and metastasis. MMPs are regulated by different cytokines, ECM proteins, and other factors. However, the molecular mechanisms by which osteopontin (**OPN**), an ECM protein, regulates ECM invasion and tumor growth and modulates MMP activation in B16F10 cells are not well defined. We have purified **OPN** from human milk and shown that **OPN** induces pro-MMP-2 production and activation in these cells. Moreover, our data revealed that **OPN**-induced membrane type 1 (MT1) MMP expression correlates with translocation of p65 (nuclear factor-kappaB (NF-kappaB)) into the nucleus. However, when the super-repressor form of IkappaBalpha (inhibitor of NF-kappaB) was transfected into cells followed by treatment with **OPN**, no induction of MT1-MMP expression was observed, indicating that **OPN** activates pro-MMP-2 via an NF-kappaB-mediated pathway. **OPN** also enhanced cell migration and ECM invasion by interacting with alphavbeta3 integrin, but these effects were reduced drastically when the MMP-2-specific **antisense** S-oligonucleotide was used to suppress MMP-2 expression. Interestingly, when the **OPN**-treated cells were injected into nude mice, the mice developed larger tumors, and the MMP-2 levels in the tumors were significantly higher than in controls. The proliferation data indicate that **OPN** increases the growth rate in these cells. Both tumor size and MMP-2 expression were reduced dramatically when anti-MMP-2 antibody or **antisense** S-oligonucleotide-transfected cells were injected into the nude mice. To our knowledge, this is the first report that MMP-2 plays a direct role in **OPN**-induced cell migration, invasion, and tumor growth and that demonstrates that **OPN** -stimulated MMP-2 activation occurs through NF-kappaB-mediated induction of MT1-MMP.

L29 ANSWER 2 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2001:541481 BIOSIS
DOCUMENT NUMBER: PREV200100541481
TITLE: Expression, roles, receptors, and regulation of osteopontin in the kidney.
AUTHOR(S): Xie, Yuansheng; Sakatsume, Minoru; Nishi, Shinichi; Narita, Ichiei; Arakawa, Masaaki; Gejyo, Fumitake (1)
CORPORATE SOURCE: (1) Department of Medicine (II), Niigata University School of Medicine, 1-757 Asahimachi-dori, Niigata, 951-8510: gejyo@med.niigata-u.ac.jp Japan
SOURCE: Kidney International, (November, 2001) Vol. 60, No. 5, pp. 1645-1657. print.
ISSN: 0085-2538.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Osteopontin (**OPN**) is a secreted glycoprotein in both

phosphorylated and non-phosphorylated forms. It contains an Arg-Gly-Asp cell-binding sequence and a thrombin-cleavage site. **OPN** is mainly present in the loop of Henle and distal nephrons in normal kidneys in animals and humans. After renal damage, **OPN** expression may be significantly upregulated in all tubule segments and glomeruli. Studies utilizing **OPN** gene-deficient mice, **antisense**-treated or anti-**OPN**-treated animals have demonstrated that **OPN** promotes accumulation of macrophages, and may play a role in macrophage-mediated renal injury, but that the effect may be mild and short-lived. On the other hand, **OPN** has some renoprotective actions in renal injury, such as increasing tolerance to acute ischemia, inhibiting inducible nitric oxide synthase and suppressing nitric oxide synthesis, reducing cell peroxide levels and promoting the survival of cells exposed to hypoxia, decreasing cell apoptosis and participating in the regeneration of cells. In addition, **OPN** is associated with renal stones, but whether it acts as a promoter or inhibitor of stone formation is controversial. It has been demonstrated that **OPN** receptors include two families: integrin and CD44. The **OPN** integrin receptors include alphavbeta3, alphavbeta1, alphavbeta5 and alpha9beta1, and alpha4beta1. In normal human kidneys, standard CD44 is expressed most dominantly. Different **OPN** functions are mediated via distinct receptors. Parathyroid hormone, vitamin D3, calcium, phosphate and some cytokines increase **OPN** expression in vitro or in vivo, whereas female sex hormones and angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists decrease **OPN** expression in some renal damage states.

L29 ANSWER 3 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4

ACCESSION NUMBER: 2002:194004 BIOSIS
DOCUMENT NUMBER: PREV200200194004
TITLE: Identification of genes related to cell phenotypic transition by differential display analysis.
AUTHOR(S): Sun Ai-Jun; Gao Ping-jin; Liu Jian-jun; Ji Kai-Da; Zhu Ding-Liang (1)
CORPORATE SOURCE: (1) Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Second Medical University, Shanghai, 200025: f97075@guomai.sh.cn China
SOURCE: Shengli Xuebao, (2001) Vol. 53, No. 6, pp. 435-439. print. ISSN: 0371-0874.
DOCUMENT TYPE: Article
LANGUAGE: Chinese

AB To identify the genes that are differentially expressed during the phenotypic transition from vascular adventitial fibroblasts to myofibroblasts, the adventitial fibroblasts were cultured from rat thoracic aorta, and myofibroblasts were obtained by treatment of fibroblasts with TGF-beta1. Differential display PCR (DD-PCR) was used to screen for differentially expressed genes by comparison of mRNA extracted from the two cell populations. Bands upregulated or downregulated on DD gels were excised, reamplified, cloned and sequenced. DD results were verified by quantitative PCR and Northern blot analysis. **Antisense** oligonucleotide was transfected to study the effect of osteopontin on migration of AF. Differential display showed a significant difference in gene expression profile between the two cell types. A transcript that was downregulated in myofibroblasts showed high DNA sequence homology to part of the gene for NADH dehydrogenase subunit 5. An upregulated transcript showed significant sequence homology to osteopontin gene. Quantitative PCR and Northern blot analysis confirmed the DD results. Among the other differential bands detected, 4 candidate sequences showed no homology to the known genes. The AF numbers of migration were significantly decreased by use of **OPN antisense** oligonucleotide. This study suggests that the downregulation of gene encoding NADH dehydrogenase subunit 5 and upregulation of osteopontin gene and several other unknown genes may be involved in the phenotypic transition of adventitial

fibroblasts to myofibroblats. Inhibition of the expression of **OPN** may play an important role in the process of vascular remodeling.

L29 ANSWER 4 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
ACCESSION NUMBER: 2000:373882 BIOSIS
DOCUMENT NUMBER: PREV200000373882
TITLE: Targeted inhibition of osteopontin expression in the mammary gland causes abnormal morphogenesis and lactation deficiency.
AUTHOR(S): Nemir, Mohamed; Bhattacharyya, Dibyendu; Li, Xiaoming; Singh, Krishna; Mukherjee, Anil B.; Mukherjee, Barid B. (1)
CORPORATE SOURCE: (1) Dept. of Biology, McGill University, 1205 Dr. Penfield Ave., Montreal, PQ, H3A 1B1 Canada
SOURCE: Journal of Biological Chemistry, (January 14, 2000) Vol. 275, No. 2, pp. 969-976. print.
ISSN: 0021-9258.
102a
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Osteopontin (**OPN**) is a sialic acid-rich, adhesive, extracellular matrix (ECM) protein with Arg-Gly-Asp cell-binding sequence that interacts with several integrins, including alphavbeta3. Since the ECM is a key regulator of mammary gland morphogenesis, and mammary epithelial cells express **OPN** at elevated levels, we sought to determine whether this protein plays a role in the postnatal mammary gland development. By generating transgenic mice that express **OPN antisense** -RNA (AS-**OPN** mice) in the mammary epithelia we achieved suppression of **OPN** production in this organ. The pregnant AS-**OPN** mice displayed a lack of mammary alveolar structures, a drastic reduction in the synthesis of beta-casein, whey acidic milk protein, and lactation deficiency. In agreement with these findings, we uncovered that a mammary cell line, NMuMG, which undergoes both structural and functional differentiation on ECM-coated plates, when transfected with an **antisense OPN**-cDNA construct, failed to undergo such differentiation. Furthermore, the results of gel-invasion assays demonstrated that these cells manifest elevated matrix metalloproteinase (MMP) activity when **OPN** expression is significantly reduced. The identity of this proteinase as MMP-2 is confirmed by Western blotting, zymography, and inhibition of its activity by a specific inhibitor, TIMP-2. Taken together, our results demonstrate, for the first time, an essential role of **OPN** in mammary gland differentiation and that the molecular mechanism(s) of its action, at least in part, involves down-regulation of MMP-2.

L29 ANSWER 5 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
ACCESSION NUMBER: 2000:123518 BIOSIS
DOCUMENT NUMBER: PREV200000123518
TITLE: Osteopontin expressed by renal tubular epithelium mediates interstitial monocyte infiltration in rats.
AUTHOR(S): Okada, Hirokazu; Moriwaki, Kenshi; Kalluri, Raghuram; Takenaka, Tsuneo; Imai, Hiroe; Ban, Shinichi; Takahama, Motohide; Suzuki, Hiromichi (1)
CORPORATE SOURCE: (1) Dept. of Nephrology, Saitama Medical College, 38 Morohongo, Moroyama-machi, Irumagun, Saitama, 350-04 Japan
SOURCE: American Journal of Physiology, (Jan., 2000) Vol. 278, No. 1 part 2, pp. F110-F121.
ISSN: 0002-9513.
102a
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In this study, we have shown that intravenously administered **antisense** oligodeoxynucleotide (ODN) was demonstrated to be taken

up by tubular epithelium, after which it blocked mRNA expression of target genes in normal and nephritic rats. Therefore, we injected osteopontin (**OPN**) **antisense** ODN to Goodpasture syndrome (GPS) rats every second day between days 27 and 35, the time when renal **OPN** expression increased and interstitial monocyte infiltration was aggravated. In parallel to blockade of tubular **OPN** expression, this treatment significantly attenuated monocyte infiltration and preserved renal plasma flow in GPS rats at day 37, compared with sense ODN-treated and untreated GPS rats. No significant changes were observed in **OPN** mRNA level by RT-PCR and histopathology of the glomeruli after ODN treatment, which was compatible with an absence of differences in the urinary protein excretion rate. In conclusion, **OPN** expressed by tubular epithelium played a pivotal role in mediating peritubular monocyte infiltration consequent to glomerular disease.

L29 ANSWER 6 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7

ACCESSION NUMBER: 2000:303524 BIOSIS
DOCUMENT NUMBER: PREV200000303524
TITLE: Elastase and matrix metalloproteinase inhibitors induce regression, and tenascin-C **antisense** prevents progression, of vascular disease.
AUTHOR(S): Cowan, Kyle Northcote; Jones, Peter Lloyd; Rabinovitch, Marlene (1)
CORPORATE SOURCE: (1) Division of Cardiovascular Research, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8 Canada
SOURCE: Journal of Clinical Investigation, (January, 2000) Vol. 105, No. 1, pp. 21-34. print.
ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Increased expression of the glycoprotein tenascin-C (TN) is associated with progression of clinical and experimental pulmonary hypertension. In cultured smooth muscle cells (SMCs) TN is induced by matrix metalloproteinases (MMPs) and amplifies the proliferative response to growth factors. Conversely, suppression of TN leads to SMC apoptosis. We now report that hypertrophied rat pulmonary arteries in organ culture, which progressively thicken in association with cell proliferation and matrix accumulation, can be made to regress by inhibiting either serine elastases or MMPs. This effect is associated with reduced TN, suppression of SMC proliferation, and induction of apoptosis. Selective repression of TN by transfecting pulmonary arteries with **antisense**/ribozyme constructs also induces SMC apoptosis and arrests progressive vascular thickening but fails to induce regression. This failure is related to concomitant expansion of a SMC population, which produces an alternative cell survival alphavbeta3 ligand, osteopontin (**OPN**), in response to pro-proliferative cues provided by a proteolytic environment. **OPN** rescues MMP inhibitor-induced SMC apoptosis, and alphavbeta3 blockade induces apoptosis in hypertrophied arteries. Our data suggest that proteinase inhibition is a novel strategy to induce regression of vascular disease because this overcomes the pluripotentiality of SMC-matrix survival interactions and induces coordinated apoptosis and resorption of matrix.

L29 ANSWER 7 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 8

ACCESSION NUMBER: 1998:489338 BIOSIS
DOCUMENT NUMBER: PREV199800489338
TITLE: Osteopontin **antisense** oligonucleotide inhibits adhesion of calcium oxalate crystals in Madin-Darby canine kidney cell.
AUTHOR(S): Yamate, T. (1); Kohri, K.; Umekawa, T.; Iguchi, M.; Kurita,

T.
CORPORATE SOURCE: (1) Dep. Urol., Kinki Univ. Sch. Med., 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511 Japan
SOURCE: Journal of Urology, (Oct., 1998) Vol. 160, No. 4, pp. 1506-1512.
ISSN: 0022-5347.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Purpose: We previously suggested that osteopontin (**OPN**) plays an important role in the process of deposited calcium crystals adhesion to cells in the early stages of urolithiasis. To further confirm this theory, we tried to inhibit **OPN** expression at the translational level and examined its cellular biological consequence on the formation and adhesion process of crystals. Materials and Methods: We synthesized **antisense** and sense oligonucleotide corresponding to an appropriate part of the coding sequence for **OPN** in Madin Darby canine kidney (MDCK) cells. With the aid of lipofection reagent DOTAP, **antisense** and sense oligonucleotide were introduced into MDCK cells grown in a confluent monolayer. After further incubation, inhibition of **OPN** expression in the cells was assessed by immunofluorescence photomicrography, and formation of calcium oxalate crystals was quantitated by incorporation of 45Ca into the stone and visualized by scanning electron microscopy (SEM). Results: **Antisense** oligonucleotide at concentrations higher than 20 muM inhibited synthesis of **OPN**. Incorporation of 45Ca into the calculus stone was inhibited by the addition of oligonucleotide in a concentration dependent manner in a range above 20 muM. More than 90% of incorporation was inhibited at 50 muM as compared to control. Inhibition of calcium crystal formation was confirmed by SEM. Conclusions: **OPN** was shown as a major component in the extracellular matrix involving the formation and adhesion of calcium crystals in the distal renal tubular cells, suggesting that **OPN** plays an important role in stimulating deposition and adhesion of calculus crystals to cells in the early stages of urolithiasis.

L29 ANSWER 8 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 9
ACCESSION NUMBER: 1997:434040 BIOSIS
DOCUMENT NUMBER: PREV199799733243
TITLE: Potential roles of osteopontin and alpha-v-beta-3 integrin in the development of coronary artery restenosis after angioplasty.
AUTHOR(S): Panda, Dibyendu; Kundu, Gopal C.; Lee, Benjamin I.; Peri, Alessandro; Fohl, David; Chackalaparampil, Isaac; Mukherjee, Barid B.; Li, Xiao D.; Mukherjee, Diane C.; Seides, Stuart; Rosenberg, Joel; Stark, Karen; Mukherjee, Anil B. (1)
CORPORATE SOURCE: (1) Sect. Dev. Genet., Heritable Disorders Branch, Building 10, Room 9S241, Natl. Inst. Child Health Human Dev., Natl. Inst. Health, Bethesda, MD 20892-1830 USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1997) Vol. 94, No. 17, pp. 9308-9313.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Angioplasty procedures are increasingly used to reestablish blood flow in blocked atherosclerotic coronary arteries. A serious complication of these procedures is reocclusion (restenosis), which occurs in 30-50% of patients. Migration of coronary artery smooth muscle cells (CASMCs) to the site of injury caused by angioplasty and subsequent proliferation are suggested mechanisms of reocclusion. Using both cultured human CASMCs and coronary atherectomy tissues, we studied the roles of osteopontin (**OPN**) and one of its receptors, alpha-v-beta-3 integrin, in the

pathogenesis of coronary restenosis. We also measured the plasma levels of **OPN** before and after angioplasty and determined the effect of exogenous **OPN** on CASMC migration, extracellular matrix invasion, and proliferation. We found that cultured CASMCs during log phase of growth and smooth muscle cell layer of the coronary atherosclerotic tissues of patients express both **OPN** mRNA and protein at a significantly elevated level compared with controls. Interestingly, whereas the baseline plasma **OPN** levels in control samples were virtually undetectable, those in patient plasma were remarkably high. We also found that interaction of **OPN** with alpha-v-beta-3 integrin, expressed on CASMCs, causes migration, extracellular matrix invasion, and proliferation. These effects were abolished when **OPN** or alpha-v-beta-3 integrin gene expression in CASMCs was inhibited by specific **antisense** S-oligonucleotide treatment or **OPN** -alpha-v-beta-3 interaction was blocked by treatment of CASMCs with antibodies against **OPN** or alpha-v-beta-3 integrin. Our results demonstrate that **OPN** and alpha-v-beta-3 integrin play critical roles in regulating cellular functions deemed essential for restenosis. In addition, these results raise the possibility that transient inhibition of **OPN** gene expression or blocking of **OPN**-alpha-v-beta-3 interaction may provide a therapeutic approach to preventing restenosis.

L29 ANSWER 9 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 10
ACCESSION NUMBER: 1997:449286 BIOSIS
DOCUMENT NUMBER: PREV199799748489
TITLE: Osteopontin **antisense** deoxyoligonucleotides inhibit bone resorption by mouse osteoclasts in vitro.
AUTHOR(S): Tani-Ishii, N. (1); Tsunoda, A.; Umemoto, T.
CORPORATE SOURCE: (1) Dep. Endodontics, Kanagawa Dent. Coll., 82 Inaoka, Yokosuka 238 Japan
SOURCE: Journal of Periodontal Research, (1997) Vol. 32, No. 6, pp. 480-486.
ISSN: 0022-3484.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Osteopontin (**OPN**) is an acidic phosphoprotein synthesized by osteoblasts and osteoclastic cells that are localized in the mineralized phase of bone matrix. **OPN** is thought to bind to the vitronection receptor on the osteoclast membrane and regulates bone resorption by the osteoclast. In this study, we investigated whether or not **OPN** can relate to osteoclast differentiation and bone resorption in a co-culture system. When C57Black/6N mouse bone marrow cells suspended on ivory slices coated with collagen were inoculated onto a MC3T3-G2/PA6 cell layer, colonies containing TRAP(+) mononuclear and multinuclear cells were formed in the presence of 1-alpha, 25-dihydroxyvitamin D-3 and dexamethasone. At the end of the culture period the number of TRAP(+) osteoclast-like cells were counted and the resorption pits were evaluated by reflected light microscopy. The mRNA of **OPN** was detected by in situ hybridization. Osteoclast-like cells expressed **OPN** mRNA. The addition of an **OPN antisense** oligomer(5' AAT CAC TGC CAA TCT CAT 3') at the start of the co-culture period decreased the number of TRAP(+) cells present after 7 d (30.3 +- 3.4 vs 56.9 +- 12.4), and the ratio of mononuclear and multinucleated cells was changed (77.6 +- 23.2 vs 60.8 +- 39.3). The total area of pits per ivory slice was also decreased by adding the **OPN antisense** oligomer (246813 vs 303139 mu-m-2). These results showed that **OPN** can be an important mechanism for regulating differentiation and bone resorption.

L29 ANSWER 10 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 11
ACCESSION NUMBER: 1996:377544 BIOSIS
DOCUMENT NUMBER: PREV199699099900
TITLE: Autocrine secretion of osteopontin by vascular smooth

muscle cells regulates their adhesion to collagen gels.
AUTHOR(S): Weintraub, Andrea S.; Giachelli, Cecilia M.; Krauss, Robert S.; Almeida, Manuela; Taubman, Mark B. (1)
CORPORATE SOURCE: (1) Box 1269, Mt. Sinai Sch. Med., One Gustave L. Levy Place, New York, NY 10029 USA
SOURCE: American Journal of Pathology, (1996) Vol. 149, No. 1, pp. 259-272.
ISSN: 0002-9440.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Osteopontin (**OPN**) is a secreted protein postulated to facilitate vascular smooth muscle cell (VSMC) adhesion and migration. Rat aortic VSMC lines were isolated after infection with recombinant retroviruses harboring **OPN** sense and **antisense** constructs. All lines grew normally in monolayer culture. On three-dimensional collagen gets, normal VSMCs and lines containing sense constructs (n = 15) or empty vector (n = 10) attached to the gel and invaded the matrix. Four of five **antisense** clones did not adhere or invade. **Antisense** clones had lower **OPN** levels after stimulation with angiotensin II than sense clones or clones containing the empty vector (**antisense**, 257 +- 102 ng/ml; sense, 473 +- 104; vector, 434 +- 66). Non-adhering **antisense** clones bad lower mean **OPN** levels after angiotensin II stimulation (161 +- 47 ng/ml) than sense or **antisense** lines with normal adhesion (486 +- 63 ng/ml). ne ability to adhere correlated with **OPN** levels gt 250 ng/ml. Adhesion and invasion were fully restored with addition of 100 to 200 ng/ml of exogenous **OPN** and were inhibited in normal VSMCs by incubation with 1 mu-g/ml anti-**OPN** antibody. The autocrine secretion of **OPN** appears to play an important role in VSMC adhesion, spreading, and invasion.

L29 ANSWER 11 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 12
ACCESSION NUMBER: 1995:317644 BIOSIS
DOCUMENT NUMBER: PREV199598331944
TITLE: Expression of **antisense** osteopontin RNA inhibits tumor promoter-induced neoplastic transformation of mouse JB6 epidermal cells.
AUTHOR(S): Su, Longcheng; Mukherjee, Anil B.; Mukherjee, Barid B. (1)
CORPORATE SOURCE: (1) Dep. Biol., McGill University, 1205 Docteur Penfield Avenue, Montreal, PQ H3A 1B1 Canada
SOURCE: Oncogene, (1995) Vol. 10, No. 11, pp. 2163-2169.
ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Elevated expression of osteopontin (**OPN**), a secreted adhesive phosphoglycoprotein, is frequently associated with many transformed cell lines of epithelial and stromal origin. Moreover, several clonal tines of preneoplastic JB6 cells derived from Balb/c mouse epidermal cultures (Colburn et al., 1978, 1979), upon treatment with 12-O-tetradecanoyl phorbol-13-acetate (TPA), become irreversibly oncogenic and concomitantly synthesize **OPN** at elevated levels (Smith and Denhardt, 1989). In the present study we sought to determine whether **OPN** expression facilitates transformation of such preneoplastic (initiated) cells. We transfected TPA-promotable JB6 c141.5a cells with an expression vector containing mouse **OPN** cDNA in **antisense** orientation under transcriptional control of dexamethasone-inducible MMTV-LTR promoter. Four stably transfected clones, which expressed drastically reduced levels of **OPN** in the presence of both dexamethasone and TPA, were characterized. We found that (a) more than 20 copies of **OPN antisense** cDNA were stably incorporated into the genome of cells from two of these clones that were examined by Southern blot analysis; (b) dexamethasone-induced expression of **antisense** **OPN** RNA prevented augmented **OPN** expression at both mRNA

and protein levels following TPA treatment; and (c) cells from all four clones failed to form colonies in soft agar medium containing both dexamethasone and TPA. Taken together, these data demonstrate that inhibition of elevated **OPN** expression blocks TPA-induced anchorage-independent growth of JB6 c141.5a cells, suggesting the possibility that **OPN** overproduction is causally related to transformation of preneoplastic cells.

L29 ANSWER 12 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 14

ACCESSION NUMBER: 1994:394133 BIOSIS
DOCUMENT NUMBER: PREV199497407133
TITLE: Specific reduction in osteopontin synthesis by **antisense** RNA inhibits the tumorigenicity of transformed Rat1 fibroblasts.
AUTHOR(S): Gardner, Humphrey A. R. (1); Berse, Brygida; Senger, Donald R.
CORPORATE SOURCE: (1) Dep. Pathol., Beth Israel Hosp., 330 Brookline Ave., Boston, MA 02215 USA
SOURCE: Oncogene, (1994) Vol. 9, No. 8, pp. 2321-2326. ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Osteopontin (**OPN**) is a secreted phosphoglycoprotein abundant in secretory luminal epithelia (Brown et al., 1992) and in bone (Reinholt et al., 1990). It contains a functional gly-arg-gly-asp- ser (GRGDS) integrin binding domain (Oldberg et al., 1986), promotes the adhesion of a variety of cell types (Somerman et al., 1989; Brown et al., 1992) and is a ligand for the vitronectin binding integrin av-beta-3 (Mivauchi et al., 1991). Elevated expression of **OPN** correlates with tumorigenic transformation in a great variety of stromal and epithelial cell lines (Senger et al., 1980, 1983, 1989; Craig et al., 1988; Chambers et al., 1992; Chang & Prince, 1993). The protein is also present in excess in the blood of patients with metastatic disease (Senger et al., 1988). To find whether **OPN** contributes significantly to the tumorigenic phenotype, we expressed **antisense** mRNA to **OPN** in high **OPN** producing malignant B77-Rat1 fibroblasts. This caused a reduction in their **OPN** secretion and reduced their ability to form both lung tumors in nude mice after intravenous injection, and colonies in soft agar. **Antisense** transfectants also showed increased spreading on vitronectin. These observations suggest that **OPN** overproduction is advantageous to the metastatic phenotype, possibly by altering adhesion via, or signal transduction from, vitronectin receptors.

L29 ANSWER 13 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 15

ACCESSION NUMBER: 1994:130408 BIOSIS
DOCUMENT NUMBER: PREV199497143408
TITLE: Reduced Malignancy of ras-transformed NIH 3T3 Cells Expressing **Antisense** Osteopontin RNA.
AUTHOR(S): Behrend, Elke I.; Craig, Ann Marie; Wilson, Sylvia M.; Denhardt, David T.; Chambers, Ann F. (1)
CORPORATE SOURCE: (1) London Regional Cancer Centre, 790 Commissioners Road East, London, ON N6A 4L6 Canada
SOURCE: Cancer Research, (1994) Vol. 54, No. 3, pp. 832-837. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Osteopontin (**OPN**) is a secreted, calcium-binding phosphoprotein that frequently has been associated with the transformed phenotype. To clarify the function of **OPN** in tumor cells, we designed experiments to: (a) express **antisense OPN** RNA in murine PAP2 cells (metastatic, ras-transformed NIH 3T3 cells) and (b)

examine the effects of **antisense OPN** expression on the tumorigenic and metastatic properties of the cells. PAP2 cells were transfected with pNMH-asOPN, an inducible, mammalian expression vector that can generate **antisense OPN** RNA complementary to the **OPN** mRNA. Two clones have been identified that expressed **antisense OPN** RNA in vitro. While reduced **OPN** protein secretion was not detected when the cells were grown in vitro, the in vivo expression of **antisense OPN** RNA was associated with reduced tumorigenicity. Tumors that did arise, with greatly extended lag time, had lost expression of **antisense OPN** RNA in vivo, suggesting that **antisense OPN** RNA expression was associated with reduced tumorigenicity of these cells.

L29 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 16
ACCESSION NUMBER: 1994:107205 BIOSIS
DOCUMENT NUMBER: PREV199497120205
TITLE: Bone sialoprotein mRNA expression and ultrastructural localization in fetal porcine calvarial bone: Comparison with osteopontin.
AUTHOR(S): Chen, J.; McKee, M. D.; Nanci, A.; Sodek, J. (1)
CORPORATE SOURCE: (1) MRC Group Periodonatl Physiol., Fac. Dentistry, Univ. Toronto, ON M5S 1A8 UK
SOURCE: Histochemical Journal, (1994) Vol. 26, No. 1, pp. 67-78. ISSN: 0018-2214.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Bone sialoprotein (BSP) and osteopontin (**OPN**) are two major non-collagenous proteins in bone that have similar biochemical properties and can mediate cell attachment through an RGD (Arg-Gly-Asp) motif that recognizes the vitronectin receptor. To facilitate evaluations of the biological functions of BSP and **OPN** in bone formation, affinity-purified rabbit polyclonal antibodies against porcine BSP and **OPN** were used, together with a high-resolution protein A-gold immunocytochemical technique to reveal the ultrastructural localization of these proteins in undermineralized sections of 50-day fetal porcine calvarial bone. In addition, 35S-labelled **antisense** riboprobes were prepared to demonstrate the cellular expression of BSP and **OPN** in the same tissues using in situ hybridization. Immunolocalization for both BSP and **OPN** revealed the highest density of gold particles associated with electron-dense organic material found at the mineralization front and in 'cement lines'. Labelling was also observed in the mineralized matrix over electron-dense material between collagen fibrils. in the osteoid of newly-formed bone, immunogold labelling for BSP and **OPN** was associated with loci of mineralization, which were often characterized by feathery clusters of fine needle-like crystals. Results of in situ hybridization on the same tissues demonstrated that BSP mRNA expression was restricted to differentiated osteoblasts with particularly strong signals evident at sites of de novo bone formation. More moderate expression of BSP was observed in 'older' osteoblasts and in some of the newly-entrapped osteocytes. Although expression of **OPN** mRNA was also observed in osteoblasts and osteocytes, the level of hybridization was similar for most bone cells and not markedly stronger than the signal observed in some stromal cells. While it is evident from these and other studies that both BSP and **OPN** are associated with bone formation, the differences observed in cellular expression indicate distinct roles for these proteins in bone formation.

L29 ANSWER 15 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 17
ACCESSION NUMBER: 1993:206907 BIOSIS
DOCUMENT NUMBER: PREV199395108132
TITLE: P21-ras and protein kinase C function in distinct and

interdependent signaling pathways in C3H 10T1/2 fibroblasts.
AUTHOR(S): Krook, Anna; Rapoport, Micha J.; Anderson, Stephen; Pross, Hugh; Zhou, Yu Chun; Denhardt, David T.; Delovitch, Terry L.; Haliotis, Tina (1)
CORPORATE SOURCE: (1) Cancer Res. Lab., Dep. Pathol., Queen's Univ., Kingston, ON K7L 3N6 Canada
SOURCE: Molecular and Cellular Biology, (1993) Vol. 13, No. 3, pp. 1471-1479.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Both p21-ras and protein kinase C (PKC) are believed to function downstream of plasma membrane-associated tyrosine kinases in cellular signal transduction pathways. However, it has remained controversial whether they function in the same pathway and, if so, what their relative position and functional relationship in such a pathway are. We investigated the possibilities that p21-ras and PKC function either upstream or downstream of each other in a common linear pathway or that they function independently in colinear signal pathways. Either decreased expression of endogenous normal ras in fibroblasts transfected with an inducible **antisense** ras construct or overexpression of a mutant ras gene reduced the capacity of the phorbol ester tetradecanoyl phorbol acetate to trigger expression of the tetradecanoyl phorbol acetate-responsive and ras-dependent reporter gene osteopontin (**OPN**). PKC depletion decreased basal **OPN** mRNA levels, and the overexpression of ras restored **OPN** expression to the level of non-PKC-depleted cells. We propose a model in which ras and PKC function in distinct and interdependent signaling pathways.

L29 ANSWER 16 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:609671 BIOSIS
DOCUMENT NUMBER: PREV200200609671
TITLE: Methods and compositions for treatment of restenosis.
AUTHOR(S): Mukherjee, Anil B.; Kundu, Gopal C. (1); Panda, Dibyendu K.
CORPORATE SOURCE: (1) Maharashtra India
ASSIGNEE: The United States of America, as represented by the Department of Health and Human Services
PATENT INFORMATION: US 6458590 October 01, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 1, 2002) Vol. 1263, No. 1, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The present invention provides sequences capable of inhibiting osteopontin (**OPN**) expression. In particular, the sequences provided herein are **antisense** osteopontin oligonucleotide sequences. The present invention further provides methods for treating restenosis using **antisense** osteopontin oligonucleotide sequences. In particular, methods for treating restenosis following vascular surgery (e.g., percutaneous transluminal coronary angioplasty (PCTA) and directional coronary atherectomy (DCA)) by using **antisense** osteopontin oligonucleotide sequences are provided.

L29 ANSWER 17 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:234397 BIOSIS
DOCUMENT NUMBER: PREV200200234397
TITLE: Growth regulation of sense and **antisense** osteopontin gene on human gliomas.
AUTHOR(S): Yang, I. (1); Jin, H. (1); Kremen, T. J. (1); Liau, L. M. (1)
CORPORATE SOURCE: (1) Division of Neurosurgery and the Jonsson Comprehensive

Cancer Center, University of California Los Angeles School of Medicine, Los Angeles, CA USA

SOURCE: Journal of Investigative Medicine, (January, 2002) Vol. 50, No. 1, pp. 79A. http://www.jinvmed.com/. print.
Meeting Info.: Meeting of the American Federation for Medical Research, Western Region Carmel, California, USA February 06-09, 2002
ISSN: 1081-5589.

DOCUMENT TYPE: Conference
LANGUAGE: English

L29 ANSWER 18 OF 23 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002283177 MEDLINE
DOCUMENT NUMBER: 22024534 PubMed ID: 12028300
TITLE: Osteopontin regulates adhesion of calcium oxalate crystals to renal epithelial cells.
AUTHOR: Yasui Takahiro; Fujita Keiji; Asai Kiyofumi; Kohri Kenjiro
CORPORATE SOURCE: Department of Urology, Nagoya City University Medical School, Mizuho-cho, Mizuho-ku, Japan.. yasui@med.nagoya-cu.ac.jp
SOURCE: INTERNATIONAL JOURNAL OF UROLOGY, (2002 Feb) 9 (2) 100-8. Journal code: 9440237. ISSN: 0919-8172.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020528
Last Updated on STN: 20020625
Entered Medline: 20020624

AB BACKGROUND: The association of calcium crystals with renal tubular cells is an important factor during the formation of urinary stones. We previously reported the strong expression of osteopontin (**OPN**) on renal tubular cells in the stone-forming kidney, suggesting that **OPN** plays a role in the crystal-cell interaction. In the present study, we examined the biological consequences of inhibiting **OPN** expression at the translational level on the formation and adhesion of crystals. METHODS: We synthesized **antisense OPN** expression vector (pTet-OPNas) using the tetracycline-regulated expression system. The pTet-OPNas was constructed using a mouse **OPN** cDNA sequence in an inverted (**antisense**) orientation. Two clones (NRK-52E/ASs) were identified by transfection of pTet-OPNas into NRK-52E cells and they showed a marked reduction of **OPN** synthesis in the absence of tetracycline. Calcium oxalate (CaOx) crystal suspension was spread homogeneously on top of the NRK-52E cells. After incubation, the association of CaOx crystals and cells was visualized by scanning electron microscopy. RESULTS: Intact NRK-52E cells, NRK-52E cells transfected with empty vector and tetracycline-treated **antisense** clones (NRK-52E/ASs), under identical conditions, were associated with CaOx crystals. In contrast, the expression of **antisense OPN** prevented the association of CaOx crystals with NRK-52E cells. CONCLUSIONS: Osteopontin plays a crucial role in the adhesion process of CaOx crystals to renal tubular cells in stone formation.

L29 ANSWER 19 OF 23 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 95305450 MEDLINE
DOCUMENT NUMBER: 95305450 PubMed ID: 7785904
TITLE: Expression of **antisense** osteopontin RNA in metastatic mouse fibroblasts is associated with reduced malignancy.
AUTHOR: Behrend E I; Craig A M; Wilson S M; Denhardt D T; Chambers A F
CORPORATE SOURCE: London Regional Cancer Centre, University of Western Ontario, Canada.

SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1995 Apr 21) 760 299-301.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950726
Last Updated on STN: 19950726
Entered Medline: 19950719

L29 ANSWER 20 OF 23 MEDLINE
ACCESSION NUMBER: 93071262 MEDLINE
DOCUMENT NUMBER: 93071262 PubMed ID: 1442213
TITLE: Development expression of bone sialoprotein mRNA in rat mineralized connective tissues.
AUTHOR: Chen J; Shapiro H S; Sodek J
CORPORATE SOURCE: MRC Group in Periodontal Physiology, Faculty of Dentistry, University of Toronto, Ontario, Canada.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (1992 Aug) 7 (8) 987-97.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921217

AB Bone sialoprotein (BSP) is a phosphorylated and sulfated glycoprotein that is a major noncollagenous protein of bone and other mineralizing connective tissues. BSP is characterized by the presence of several polyglutamic acid segments and an RGD motif that mediates cell attachment through a vitronectin-like receptor. Although the precise function of BSP is unknown, the expression of BSP in conjunction with bone formation in vitro indicates a role for this protein in the biomineralization of connective tissues. In this study we used Northern hybridization and in situ hybridization to determine the tissue-specific and developmental expression of BSP during embryogenesis and growth of rat tissues. Analysis of tissues obtained from 13, 17, and 21 day fetuses, and from 4-, 14-, and 100-day-old animals indicates that BSP mRNA expression is restricted to cells actively forming the mineralizing tissues of bone, dentin and cementum. BSP mRNA transcripts were first evident in fully differentiated osteoblasts of 17 day fetal tissues at sites of de novo intramembranous and endochondral bone formation, with maximal expression observed at 21 days of gestation. Thereafter, BSP mRNA levels decreased markedly, and in adult bone hybridization was detected only in the primary spongiosa of long bones. In comparison, mRNAs for osteopontin (**OPN**), alkaline phosphatase (ALP), and osteocalcin (OC) peaked at 4-14 days postpartum before declining. In the tibiae, Northern hybridization revealed a second peak of mRNA for BSP, ALP, and **OPN** at 14 days, reflecting an increased osteogenic activity due to the formation of the secondary centers of ossification in the epiphyseal cartilage. In situ hybridization also revealed BSP mRNA in hypertrophic chondrocytes at sites of bone formation, in odontoblasts of the incisor during dentinogenesis, and in cementoblasts during cementogenesis. In view of the restricted distribution and temporal changes in the expression of BSP mRNA that we observed together with the chemical properties of BSP, we believe that this protein has a specific role in mediating the initial stages of connective tissue mineralization.

L29 ANSWER 21 OF 23 CAPLUS

ACCESSION NUMBER: 2002:630210 CAPLUS
DOCUMENT NUMBER: 137:182807
TITLE: The role of Cbfal in gene expression of matrix proteins and odontogenesis
AUTHOR(S): Kitamura, Yoshiko
CORPORATE SOURCE: Grad. Sch. Dent., Okayama Univ., Japan
SOURCE: Okayama Shigakkai Zasshi (2002), 21(1), 117-129
CODEN: OSZAE3; ISSN: 0913-3941
PUBLISHER: Okayama Shigakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The odontogenesis of dental germs and the expression of the dental matrix protein genes were examd. using a knocked out mouse. The odontogenesis wa obsd. at viviparous 17.5 days, and 0, 2.5 and 8 days after birth using an electron microscope. The expression was obsd. using an in-situ hybridization method. Digoxigenin-11-UTP-labeled RNA probes of sense and **antisense** chains were used in the hybridization with mRNA. The probes were detected using an alk. phosphatase-labeled anti-Digoxigenin antibody. In the incisor and the molar, as results, the phases of differentiating papilla cells, predontoblast, young odontoblast, old and short odontoblasts, pre-ameloblast, presecretory ameloblast were obsd. at the 17.5 days to the 2.5 days. A matrix-forming phase was obsd. in the amelogenesis. The short ameloblast was obsd. at 8 days after birth. The mRNAs of Cbfal, Col I, OSN, **OPN**, OSC, DSPP, and AG were detected. In the incisor of the knocked out mouse, a bell-like form only was obsd. and odontoblast-like and ameloblast-like cells were found in there. The mRNAs of Col I, OSN, and DSPP were detected at the 17.5 days and the 0 day. Those of other signal proteins were for the first time detected at the 0 day. In the molar, the dental germ wa in bud-like to hat-like forms also in the 0 day. The mRNAs of OSN, **OPN**, OSC, DSPP, and AG were not detected in each phase. The role of Cbfal in the odontogenesis and the gene expression was discussed.

L29 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:97107 CAPLUS
DOCUMENT NUMBER: 134:188560
TITLE: Regulation of osteopontin expression by its **antisense** RNA in renal epithelial cells
AUTHOR(S): Chen, Yong-xiong; Li, Jin-hua; Yu, Xue-qing; Huang, Ling-hong; Chen, Wei-ying; Lu, Jun; Fan, Chong-lun; Yin, Pei-da
CORPORATE SOURCE: Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University of Medical Sciences, Canton, 510080, Peop. Rep. China
SOURCE: Zhongguo Bingli Shengli Zazhi (2000), 16(11), 1153-1158
CODEN: ZBSZEB; ISSN: 1000-4718
PUBLISHER: Jinan Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Studies were carried out to investigate the effect of **antisense** RNA on osteopontin (**OPN**) expression in renal tubular epithelial cells. Cell clone expressing stably **OPN antisense** RNA was formed by transferring retroviral vector expressing **OPN antisense** RNA into renal tubular epithelial cells, NRK52E cells, using liposomes, with cell clones transfected by empty vector and vector expressing **OPN** sense RNA as controls. RNase protection assay (RPA), Western Blot, ELISA and assay of **OPN** activity were performed to detect expression of **OPN** mRNA and protein in above clones cultured with or without epidermal growth factor(EGF). The **antisense** RNA was only expressed by **antisense** clone. **Antisense** clone, sense clone and empty clone all expressed **OPN** mRNA. EGF enhanced expression of **OPN** mRNA, but not **OPN antisense** RNA or **OPN** sense RNA in above

clones. **OPN** protein was not expressed in **antisense** clone cultured with or without EGF and empty clone cultured without EGF, but was expressed in sense clone cultured with or without EGF and empty clone cultured with EGF. **Antisense** RNA can inhibit **OPN** protein expression by preventing **OPN** mRNA translation, but not inhibit **OPN** mRNA transcription in renal tubular epithelial cells.

L29 ANSWER 23 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95338774 EMBASE
DOCUMENT NUMBER: 1995338774
TITLE: Osteopontin (**OPN**) may facilitate metastasis by protecting cells from macrophage NO-mediated cytotoxicity: Evidence from cell lines down-regulated for **OPN** expression by a targeted ribozyme.
AUTHOR: Feng B.; Rollo E.E.; Denhardt D.T.
CORPORATE SOURCE: Nelson Biological Laboratories, PO Box 1059,Piscataway, NJ 08855, United States
SOURCE: Clinical and Experimental Metastasis, (1995) 13/6 (453-462).
ISSN: 0262-0898 CODEN: CEXMD2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Osteopontin (**OPN**) is a GRGDS-containing phosphoglycoprotein that is capable of facilitating cell adhesion and modulating gene expression via integrin receptors. Three hammerhead ribozymes designed to target three different regions of **OPN** mRNA were shown to cleave the message catalytically in vitro. Plasmid vectors that had been engineered to express the ribozymes in mammalian cells were used to generate stably transfected T24 H-ras-transformed NIH3T3 cells that normally express **OPN** at high levels. Northern and Western blot analyses showed that **OPN** mRNA and protein expression were reduced in a subset of these anti-**OPN** ribozyme-expressing cell lines. Cells whose ability to produce **OPN** had been impaired exhibited greater sensitivity to the cytotoxic action of activated RAW264.7 macrophage-like cells; they were also less effective at suppressing macrophage NO production. In agreement with previous reports, they were also less tumorigenic and metastatic in an experimental metastasis assay. These results are consistent with the hypothesis that **OPN** serves as a defense against NO-mediated host cell cytotoxicity and thereby augments the metastatic phenotype.

L31 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2000:303524 BIOSIS
DOCUMENT NUMBER: PREV200000303524
TITLE: Elastase and matrix metalloproteinase inhibitors induce regression, and tenascin-C antisense prevents progression, of vascular disease.
AUTHOR(S): Cowan, Kyle Northcote; Jones, Peter Lloyd; Rabinovitch, Marlene (1)
CORPORATE SOURCE: (1) Division of Cardiovascular Research, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8 Canada
SOURCE: Journal of Clinical Investigation, (January, 2000) Vol. 105, No. 1, pp. 21-34. print.
ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Increased expression of the glycoprotein tenascin-C (TN) is associated with progression of clinical and experimental pulmonary hypertension. In cultured smooth muscle cells (SMCs) TN is induced by matrix metalloproteinases (MMPs) and amplifies the proliferative response to growth factors. Conversely, suppression of TN leads to SMC apoptosis. We now report that hypertrophied rat pulmonary arteries in organ culture, which progressively thicken in association with cell proliferation and matrix accumulation, can be made to regress by inhibiting either serine elastases or MMPs. This effect is associated with reduced TN, suppression of SMC proliferation, and induction of apoptosis. Selective repression of TN by transfecting pulmonary arteries with antisense/**ribozyme** constructs also induces SMC apoptosis and arrests progressive vascular thickening but fails to induce regression. This failure is related to concomitant expansion of a SMC population, which produces an alternative cell survival alphavbeta3 ligand, osteopontin (**OPN**), in response to pro-proliferative cues provided by a proteolytic environment. **OPN** rescues MMP inhibitor-induced SMC apoptosis, and alphavbeta3 blockade induces apoptosis in hypertrophied arteries. Our data suggest that proteinase inhibition is a novel strategy to induce regression of vascular disease because this overcomes the pluripotentiality of SMC-matrix survival interactions and induces coordinated apoptosis and resorption of matrix.

L31 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 1995:550855 BIOSIS
DOCUMENT NUMBER: PREV199698565155
TITLE: Osteopontin (**OPN**) may facilitate metastasis by protecting cells from macrophage NO-mediated cytotoxicity: Evidence from cell lines down-regulated for **OPN** expression by a targeted **ribozyme**.
AUTHOR(S): Feng, Bo; Rollo, Ellen E.; Denhardt, David T. (1)
CORPORATE SOURCE: (1) Nelson Biol. Lab., PO Box 1059, Piscataway, NJ 08855 USA
SOURCE: Clinical & Experimental Metastasis, (1995) Vol. 13, No. 6, pp. 453-462.
ISSN: 0262-0898.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Osteopontin (**OPN**) is a GRGDS-containing phosphoglycoprotein that is capable of facilitating cell adhesion and modulating gene expression via integrin receptors. Three hammerhead **ribozymes** designed to target three different regions of **OPN** mRNA were shown to cleave the message catalytically in vitro. Plasmid vectors that had been engineered to express the **ribozymes** in mammalian cells were used to generate stably transfected T24 H-ras-transformed NIH3T3 cells that normally express **OPN** at high levels. Northern and Western blot analyses showed that **OPN** mRNA and protein expression were

reduced in a subset of these anti-**OPN ribozyme** -expressing cell lines. Cells whose ability to produce **OPN** had been impaired exhibited greater sensitivity to the cytotoxic action of activated RAW264.7 macrophage-like cells; they were also less effective at suppressing macrophage NO production. In agreement with previous reports, they were also less tumorigenic and metastatic in an experimental metastasis assay. These results are consistent with the hypothesis that **OPN** serves as a defense against NO-mediated host cell cytotoxicity and thereby augments the metastatic phenotype.

L35 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107136 CAPLUS
DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the **wound response** by **thrombospondin 2** or osteopontin
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009735	A2	20020207	WO 2001-US24147	20010731
WO 2002009735	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002048577	A1	20020425	US 2001-919770	20010731

PRIORITY APPLN. INFO.: US 2000-222071P P 20000801

AB The invention provides methods of modulating the amt. and/or biol. activity of **thrombospondin 2** or osteopontin in an animal. The methods comprise the step of introducing into the animal an amt. of osteopontin, and/or a **thrombospondin** (2) antagonist, effective to modulate the amt. or biol. activity of **thrombospondin** (2) or osteopontin in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amt. of an agents or antagonist of a matricellular protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or implanted within, the soft tissue of an animal.

L36 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107136 CAPLUS
DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the **wound response** by thrombospondin 2 or **osteopontin**
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009735	A2	20020207	WO 2001-US24147	20010731
WO 2002009735	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002048577	A1	20020425	US 2001-919770	20010731

PRIORITY APPLN. INFO.: US 2000-222071P P 20000801

AB The invention provides methods of modulating the amt. and/or biol. activity of thrombospondin 2 or **osteopontin** in an animal. The methods comprise the step of introducing into the animal an amt. of **osteopontin**, and/or a thrombospondin (2) antagonist, effective to modulate the amt. or biol. activity of thrombospondin (2) or **osteopontin** in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amt. of an agents or antagonist of a matricellular protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or implanted within, the soft tissue of an animal.

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